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PROBLEMS INVOLVED IN THE HOMOTRANSPLANTATION OF TISSUES, WITH PARTICULAR REFERENCE TO SKIN*

BY

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[WITH SPECIAL PLATE]

When tissue is removed from an animal and transferred to another part of the same animal the process is referred to as autotransplantation; homotransplantation consists in the transfer of tissue from one animal to another of the same species. It has been found that, with the exception of cornea, cartilage, and blood vessels, all homotransplants undergo complete disintegration at varying time intervals.

During the last war a stage was reached when there developed a great demand for skin replacement in burned casualties—an urgent demand, therefore, for a skin bank. Setting out to elucidate the nature of the constant disintegration of homotransplanted skin, P. B. Medawar made many important observations and laid a sound experimental approach to this subject. Further work is necessary, as the homotransplant problem is not an obscure section of pure research; there is an increasing clinical demand for its solution.

That homotransplanted tissue disintegrates is not generally appreciated, perhaps because a great deal of Medawar's work was published in non-clinical journals during the latter war years. Medawar (1943–4), who has thrown more light than anyone else on the processes involved in skin homotransplantation, has this to say: "The plastic surgeon has in the past relied upon the laboratory worker neither for inspiration, principle, nor technical aid." I wish, therefore, to take the opportunity to review some of the significant work that has been carried out on homotransplantation in general and of skin in particular.

John Hunter was very interested in the behaviour of transplanted tissues and carried out numerous experiments himself, though none of his personal observations on the higher animals is still valid for us to-day; his work on the homotransplantation of teeth, for example, was not confirmed by his contemporaries, and fell into disrepute (Palmer, 1835). However, although John Hunter has nothing illuminating to say on the homotransplantation of tissues, his experimental approach to surgical problems remains an inspiration to modern surgery. There can be no doubt that the problems of homotransplantation can be solved only by animal experiments—a method fundamental in the teachings of John Hunter.

*Based on an Arris and Gale Lecture delivered at the Royal College of Surgeons of England on February 2, 1951.

Homotransplantation of Embryonic Tissues

Homotransplantation of tissue is successful in the lower orders of animal life and becomes increasingly unsuccessful as one ascends the phylogenic scale. Resistance to foreign tissue is most highly developed in the mammalian group.

From the ontogenetic point of view, the embryo at certain stages has little or no resistance to alien tissue. Thus the early chick chorio-allantoic membrane is a willing host to many tissues which may be placed on it. One might infer from this that embryonic tissue is deficient in the power to produce antibodies; perhaps because it lacks a fully developed reticulo-endothelial system. On the other hand, the immunity response to homotransplanted embryonic tissue varies at different stages of development of that tissue, as was shown by Burke and his co-workers (1944), who found that "antigens having adult organ specificity do not appear until the organs are well differentiated morphologically."

The relative lack of resistance to alien tissue on the part of the embryo and the mild reaction to homotransplanted embryonic tissue have led to many exaggerated statements and great expectations. Willis (1935) has fairly reviewed the situation and set it in its correct perspective: "Embryos or parts of embryos, implanted whole or minced or pulped into the adult animals of like species, may suffer any of three fates: (1) the tissue may be rapidly and completely absorbed, or (2) they may survive, grow, and differentiate for some days or weeks, and then suffer resorption, or (3) they may grow to considerable masses of mixed differentiated tissues which may persist for long periods, even for the lifetime of the host animal. . . . The results vary with the species of animal, the age and degree of subdivision of the embryo tissue introduced, the site of implantation and probably the age, health, and other personal peculiarities of the host animal."

It is therefore fair to say that no greater hope of success can be expected from embryonic than from adult tissue. The fate of minced tissues is of no interest to us as surgeons. We are interested in homotransplantation not because of the histological changes but because we wish to study the possibilities of homotransplanting whole organs which will function in their new sites. I would say, therefore, that experiments in homo-

transplanting tissues which do not take into account the natural conditions of that tissue are a waste of time. A kidney, for example, requires an adequate blood supply and clear drainage for its urine—otherwise it will not function when autotransplanted, let alone homotransplanted. Tumour implantation has, of course, produced a great many valuable data, but this work is in a different category.

Review of Past Theories of Homotransplant Failure

In reviewing past theories which sought to explain the nature of the disintegrative process it is convenient to start with Ehrlich's theory of athrepsia. It should be pointed out at this stage that a great deal of the general theory of homotransplant disintegration has been built up from experiments with neoplastic tissues, and most of the following theories are therefore inextricably bound up with observations on tumour growth.

1. The Theory of Athrepsia

Ehrlich postulated a lack of nutriment in the host after having observed an increase in the percentage of takes in successive transfers of certain homotransplantable tumours. The modern interpretation of this phenomenon suggests that through successive transfers simplification of the antigens occurs and the surviving cells withstand the immunity reaction of the host. There are many reasons for discarding Ehrlich's point of view, and perhaps chief among them are these: (*a*) mice can be rendered susceptible to transplantation of tumours and to leukaemias by total body irradiation of the host prior to transplantation (Murphy, 1926; Krebs *et al.*, 1930; Furth *et al.*, 1933; Richter and MacDowell, 1935); (*b*) trypan blue injected daily into rabbits can render them susceptible to certain transplanted tumours (Saphir and Appel, 1943); and (*c*) human skin can grow in serial fashion on the chorio-allantoic membrane of the chick (Blank *et al.*, 1948).

2. The Theory of Natural Immunity

On the analogy of blood group incompatibility it has been argued that there is a natural incompatibility of other tissues too. This theory, however, has not been supported by experimental evidence. Medawar (1946) has shown that there exists no antigenic relationship between the red cells and skin in rabbits. But it is not known whether there are natural iso-antibodies reacting with the fixed tissues but not with the red cells. The available evidence for and against this theory of natural immunity has been adequately reviewed by Medawar (1943–4). Gorer is convinced that natural iso-antibodies of the red cells may be shared also by the fixed tissues. At the moment we have no sound evidence that natural antibodies play any part in the destruction of homotransplants.

3. The Theory of Lack of Stroma and Vascular Supply

This theory has received no experimental proof. Medawar (1948) has shown that if a rabbit is specifically immunized against the skin of a given donor and later receives a skin homotransplant into the anterior chamber of its eye, the homotransplant will be destroyed only if it is invaded by blood vessels. Thus, Medawar concluded: "The fact that vascularized eye implants are destroyed, though they are not dependent on a blood supply for continued survival, shows that vascular stagnation is not causally connected with the breakdown of skin homografts."

Of course, this is not to deny that rupture of blood vessels does occur in a homotransplant, but it does so only after the disintegrative process has set in. It has been clearly shown by Medawar and others that first-crop skin homotransplants become well vascularized and only later undergo disintegration. Furthermore, kidney homotransplants show signs of disintegration before the blood supply fails.

4. The Theory of Local Cellular Reaction

Leo Loeb, J. B. Murphy, and others have advanced this theory for many years, and it cannot be said to have been universally discarded—particularly in the U.S.A. Loeb (1944) has recently restated his whole case in a very comprehensive volume. His general theory is difficult to follow and involves metaphysical concepts referred to as "differentials" which call forth the production of immune substances *locally* at the site of the homotransplant; these "differentials" can be organismal, individual, or tissue-specific. It would be difficult to find him giving a more comprehensible exposition than this: "The nature of the organismal differentials depends upon the genetic constitution of individuals and species and large groups, and further analysis has shown that multiple factors determine the character of the individuality differential. These genetic factors lead to the production of substances which, when introduced into organisms possessing different organismal differentials, cause incompatibilities between host and transplant" (Loeb and King, 1935).

Loeb regards "differentials" as direct cytotoxins; his main contention is that the round-cell infiltration which occurs around the homotransplant is the main reaction of the host—that is, he denies a significant systemic reaction. Other workers, who support other theories, interpret the "differentials" as merely equivalent to tissue antigens. Thus, for instance, Burnet and Fenner (1948) point out: "There is little in Loeb's work, however, which could not be interpreted in terms of the immune response as the principal mechanism, and not a secondary effect. It appears to us that the 'individuality differentials' of which he speaks are in fact the antigens of the grafted tissue relative to the particular host concerned."

J. B. Murphy (1926) follows the same line of thought as Loeb: "The accumulation of the small round-cell infiltration about foreign tissue introduced into the higher animals is a constant finding and has been noted and commented upon by many investigators." Blumenthal (1941), in a series of experiments on different animals, confirmed the local cellular aggregation of lymphocytes but also found a lymphocytosis in the peripheral circulation. A criticism of this theory is that it concentrates too much on mere histology. Darcy (1949), using pieces of submaxillary gland, found evidence that the plasma cell comes to dominate the histological picture as the homotransplant disintegrates more and more. One has to be cautious about histological evidence from tissues homotransplanted without any attempt to establish a vascular supply to them.

It must be said that experience gained from homotransplanting kidneys convinces me of the futility of depending on a wholly histological interpretation of disintegration. Fig. 1 (Special Plate), for instance, shows a kidney removed five days after homotransplantation; vascular anastomosis was carried out by interposing the kidney on the carotido-jugular circulation of the host dog. It will be immediately obvious that there is a complete disintegration of the kidney parenchyma where a complex cellular infiltration has occurred. But what conclusions can be drawn from such a histological picture? Furthermore, experience in homotransplanting skin convinces one of the complete lack of any consistent mesenchymal cell reaction.

A great deal of recent work tends to refute completely the theory of the local cellular reaction of Loeb. Morgan Harris (1943) has shown that "rat and mouse cells apparently are physiologically compatible *in vitro*. Toxic phenomena were completely absent in mixed cultures, and both rat and mouse cells remained normal in cytological appearance." In addition, the whole of Medawar's work and our own cannot be interpreted in terms of the local cellular reaction theory. Homotransplant disintegration is to-day interpreted as an actively acquired immunity reaction; this concept is gaining more and more support from experimental evidence.

FIG. 1.—Section of a homotransplanted kidney in dog, removed on fifth day. (H. and E. ×107.)

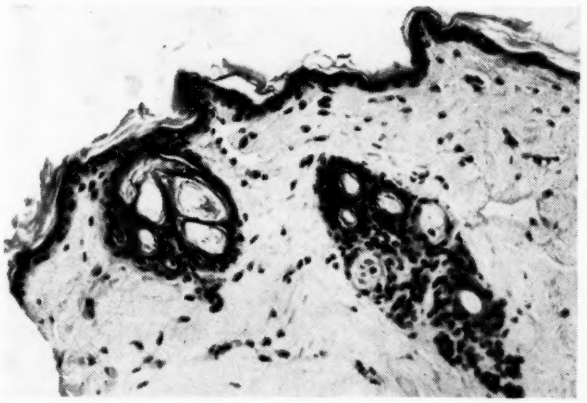

FIG. 2.—Section of rabbit skin before transplantation. (H. and E. ×140.)

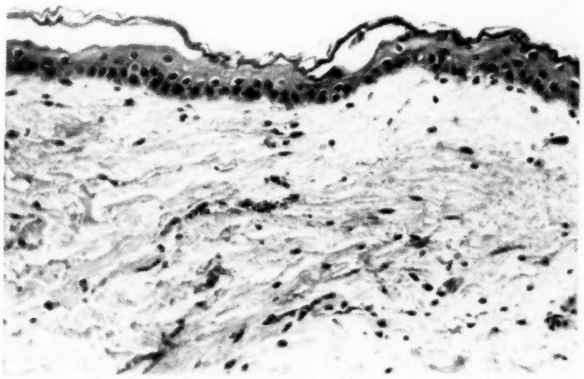

FIG. 3.—Section of skin 4 days after autotransplantation. (H. and E. ×140.)

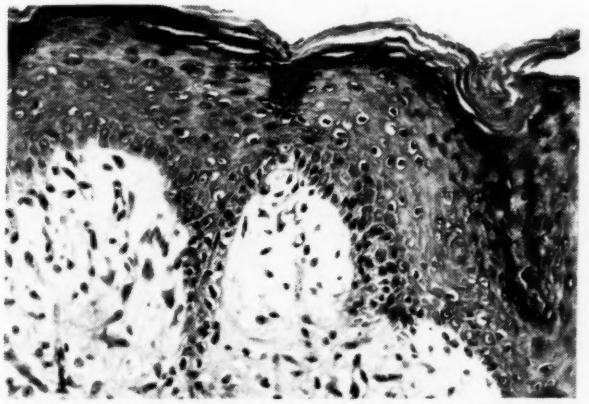

FIG. 4.—Section of skin 16 days after autotransplantation. (H. and E. ×140.)

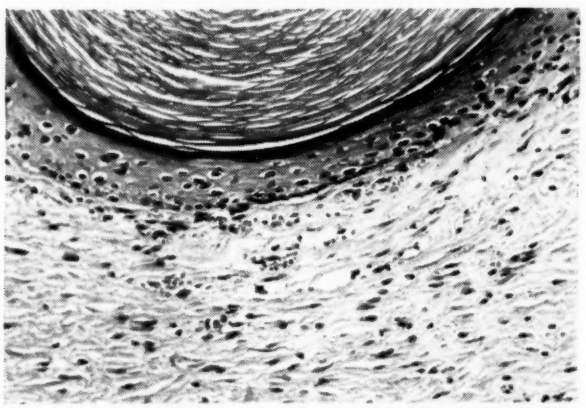

FIG. 5.—Section of skin 24 days after autotransplantation. (H. and E. ×140.)

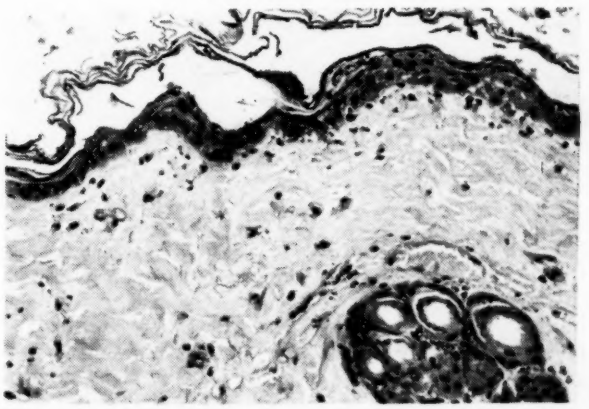

FIG. 6.—Section of skin 8 days after homotransplantation. (H. and E. ×140.)

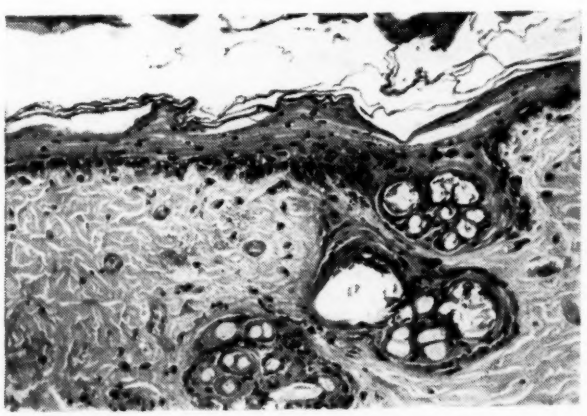

FIG. 7.—Section of skin 12 days after homotransplantation. (H. and E. ×140.)

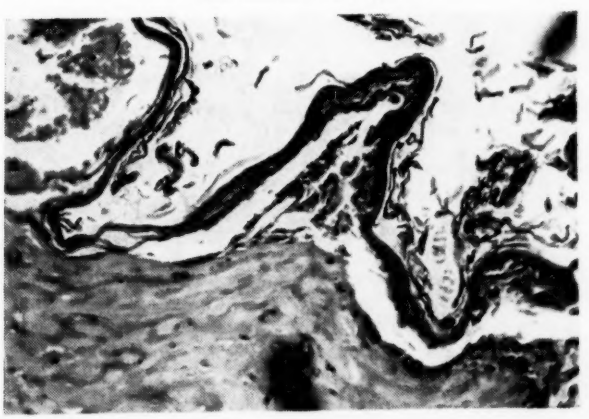

FIG. 8.—Section of skin 16 days after homotransplantation. (H. and E. ×140.)

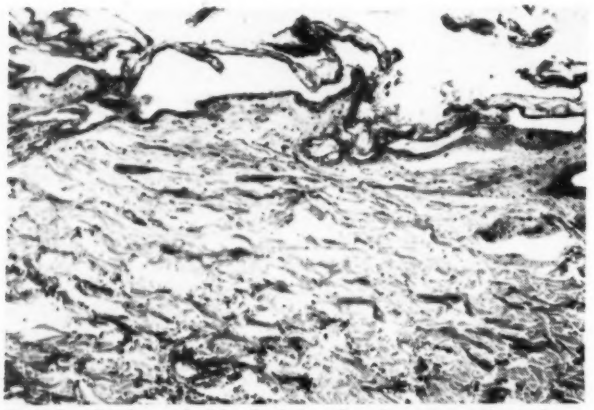

FIG. 9.—Section of skin 2 days after homotransplantation; second crop. (H. and E. ×140.)

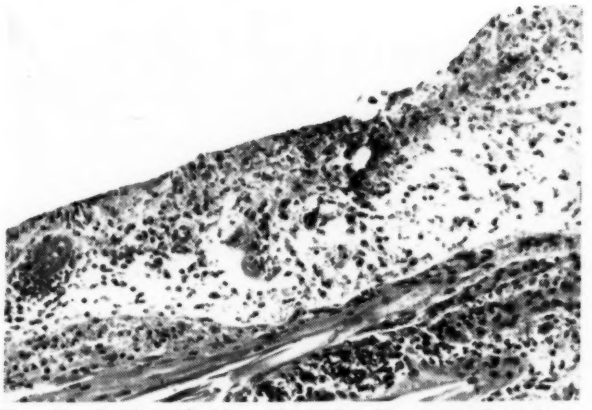

FIG. 10.—Section of skin 6 days after homotransplantation; second crop. (H. and E. ×140.)

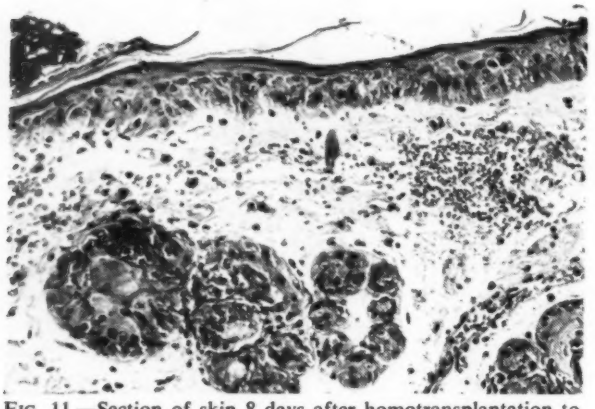

FIG. 11.—Section of skin 8 days after homotransplantation to irradiated host. (H. and E. ×140.)

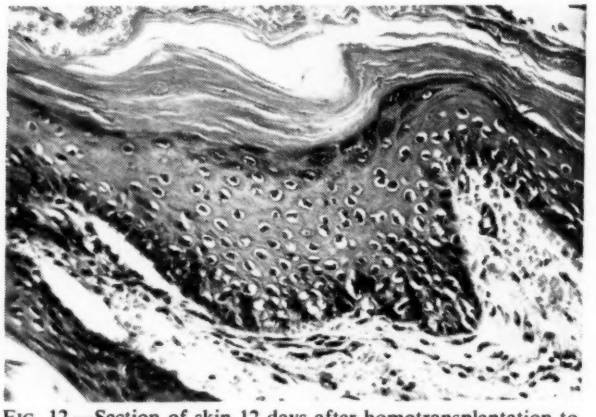

FIG. 12.—Section of skin 12 days after homotransplantation to irradiated host. (H. and E. ×140.)

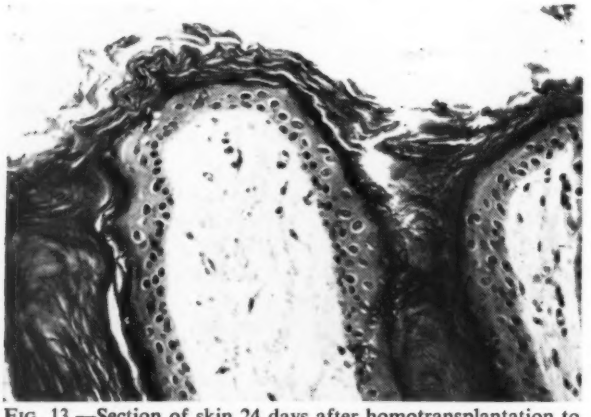

FIG. 13.—Section of skin 24 days after homotransplantation to irradiated host. (H. and E. ×140.)

FIG. 14.—Section of skin 4 days after homotransplantation to previously irradiated animal; second crop. (×102.)

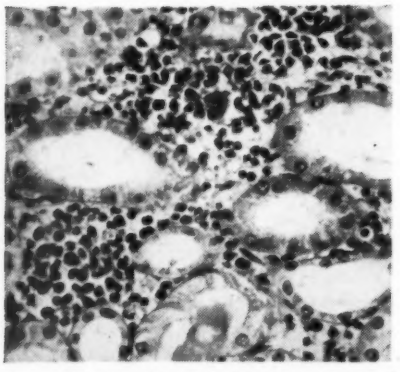

FIG. 15.—Section of homotransplanted kidney: healthy tubules with intercellular round-cell infiltration of mixed type. (H. and E. ×208.)

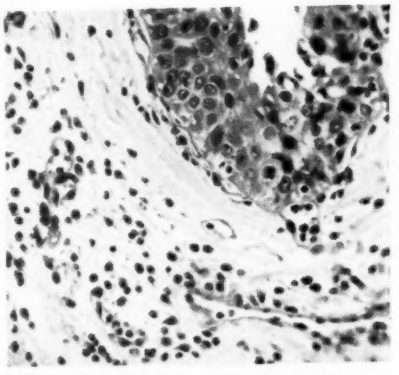

FIG. 16.—Section of ureter of same homotransplanted kidney: mitosis in mucosal cells; round-cell infiltration in submucosa. (H. and E. ×173.)

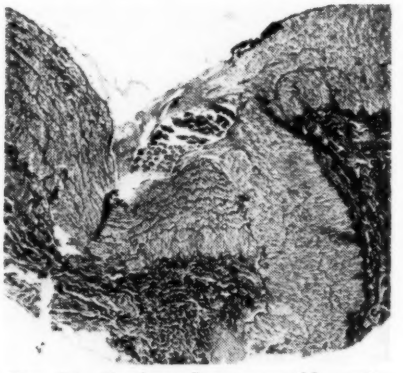

FIG. 17.—Section of reno-carotid anastomosis of same kidney. Healing occurring; no sign of round-cell infiltration. (Verhoef's elastic stain; counter-stained with Van Gieson. ×42.)

The Theory of Actively Acquired Immunity

Any theory of an actively acquired immunity would be obliged to demonstrate that a second crop of homotransplants from the same donor to the same recipient would disintegrate at a faster rate than the first.

Using the skin of rabbits, Medawar (1944) demonstrated that second-crop homotransplants from the same donor to the same recipient disintegrated at a faster rate than those of the first crop. Loeb and his school, in spite of repeated experiments, had not been able to show this, although they tried to find evidence of this reaction. Their failure can be explained by the fact that they used different donors for the second crop of homotransplants (Burnet and Fenner, 1948). Gibson and Medawar (1943), by eliminating this error and using the same donor and recipient for first and second crops, showed that "the breakdown of foreign epithelium is an immunity reaction. The absence of a demonstrable cellular mechanism, the time relations of the process as a whole, and the accelerated regression of foreign skin epithelium are brought about by a mechanism conforming to the general pattern of an antigen–antibody reaction."

In elaborating this theory a brief outline of the experimental method used will be of help. The use of skin in elucidating the nature of the disintegration of homotransplanted tissue is both convenient and sound. The main criterion of a method of analysis of the behaviour of homotransplanted tissue is that the original natural conditions of the tissue should be recapitulated so far as possible in the new site. Skin answers this criterion, for an adequate capillary blood supply develops in four days—the time for primary healing.

The method to be outlined now is essentially that described by Medawar (1944). Full-thickness skin grafts are removed from a rabbit and transferred to another. The host rabbit has an area of skin removed from its thorax, which forms a bed for the homotransplants. A dressing of petroleum jelly and gauze is then applied, being kept in position by a light plaster-of-Paris cast. This cast causes no inconvenience to the rabbit.

The control for the homotransplant experiment is the natural history of the autotransplant. Figs. 2–5 show that in the case of the autotransplant a gradual thickening of epithelium occurs, reaching a maximum at about the sixteenth day and then slowly subsiding to normal at about the thirtieth day. Against this control is placed the natural history of the homotransplant at a given dosage of 0.45 g. of skin (see below). Figs. 6–8 show that a less vigorous thickening of the epithelium occurs in the case of the homotransplant, where the average length of survival is only about 10 days.

From these sections it is clear that there is an absence of a mesenchymal cell reaction in both cases; most of the round cells are polymorphs, which appear to be merely part of the healing process.

Figs. 9 and 10 show the natural history of the second-crop homotransplants—that is, where the donor and the recipient are the same as in the first crop. The homotransplants of the second crop do not die immediately, but the length of their survival is now reduced to less than six days.

The Dosage Factor

Medawar (1944) has stressed the importance of the dosage of skin in relation to survival time; the greater the dosage the faster is the disintegration. It is necessary to use small doses of skin to demonstrate an actively acquired immunity reaction. Medawar used doses of 0.25 g. and 0.45 g. of skin. Our own experience with rabbits shows that skin homotransplanted at a dose of 0.9 g. and over is dead by the fourth day. The dosage factor may be confined to skin, as it is certainly not an important factor in homotransplanting kidneys.

Antigens and Antibodies

If one is to accept that there is an actively acquired immunity reaction involved in the homotransplant disintegrative process, it will be of help to remind ourselves of the nature of antigens and antibodies. Furthermore, it will be necessary to determine just how closely the tissue reaction parallels the bacterial antigen–antibody reaction. Even if an antigen–antibody reaction is admitted, that does not explain the details of the homotransplant disintegrative process. Medawar is of the opinion that the homotransplant reaction is akin to the Arthus phenomenon. This opinion, however, still remains purely speculative.

The Nature of Antigen

What is the nature of antigen? Burnet and Fenner (1948) state: "An antigen is a molecular species, either free or incorporated in the substance of an organism, which when introduced parenterally into a suitable mammalian host . . . gives rise to a specific change in the host which may be either the development of antibody in the blood or some form of species tissue reactivity."

An antigen is usually a foreign protein: Heidelberger (1936) has shown that polysaccharides are also antigenic; Lumsden (1938) has suggested that lipoids in the cells of carcinoma may exist in a state which makes them readily antigenic. Evidence is accumulating that tissue antigen is derivative from the gene, but the relationship is not clear. Gorer (1938) claims that "antigenic differences are determined by dominant genes."

The relationship between antigen and gene allows one to conclude that the basic laws of homotransplant disintegration, if indeed they conform to the general pattern of an antigen–antibody reaction, operate for normal and neoplastic tissues alike, since both have a genetic pattern. Gorer (1942a) states: "The laws governing the transplantation of normal and neoplastic tissues are essentially the same. Within populations rendered almost completely homogeneous by brother–sister inbreeding, the successes obtained approximate closely to those of autotransplantation."

Eisen and Woglom (1941) agree in principle: "Thus acquired resistance to transplantable tumours depends upon the genetic differences between the animal inoculated and the one that originally produced the neoplasm, and is not specifically directed against the malignant cell."

Phelps (1937) confirms this: "The antigen in cancer cells which gives rise to the antibodies is not peculiar to malignant cells . . . the antibodies are probably isoantibodies formed in response to injections of foreign, though homologous, cells."

That there is a genetic basis involved in tissue incompatibility is shown in those few instances in which successful skin homotransplantation has been performed between uniovular twins in whom there is an identical genetical make-up (Padgett, 1932; Brown, 1937). McIndoe and Franceschetti (1950) have employed the

principle to identify two uniovular twins out of three children about whose exact identity there was some confusion soon after birth.

It has been shown that an exact genetic make-up is not absolutely necessary for successful homotransplantation. Skin can be successfully grafted between dizygotic (non-identical) twins in cattle (Billingham and Medawar, 1950, personal communication). It appears that twin cows, whether uniovular or not, are synchorial; their circulations *in utero* are confluent and they are born with identical blood groups, as Owen's work has shown. Successful ovarian homotransplants have been carried out between mice strains having only one gene difference (Russell and Hurst, 1945). Burnet and Fenner (1948), in this connexion, refer to a communication from Medawar and McDonald stating that "skin transplanted between related but not homozygous mice can sometimes survive despite clear evidence of an immune response."

These results tend to support the theory that perhaps only a few genes are involved in tissue incompatibility. Such genes have been referred to by Snell (1948) as histocompatibility genes. Gorer (1942a) believes that "the host reacts to antigens present in the donor's tissue but absent from its own; it does not matter if the host possesses antigens that are lacking in the donor's tissue."

The Nature of Antibody

What is the nature of antibody? Burnet and Fenner (1948) define it as follows: "Antibody as normally observed consists of molecules of serum globulin which differ from other such molecules in combining readily with the corresponding antigen . . . but not with unrelated substances. Antibody is usually similar to the gamma globulin."

To what extent do tissue antigens and antibodies parallel the behaviour of their bacterial counterparts? Antibodies to bacterial antigens are usually demonstrable in the serum by precipitin reactions, a notable exception being the tuberculin reaction in respect of which no antibodies have been demonstrated in the serum of animals receiving injections of this material. So far, no antibodies have been clearly demonstrated beyond all reasonable doubt in the serum of animals which have received homotransplants of normal tissue. Woodruff and Forman (1950) claim to have done this: "It is apparent that after a Wistar rat has received a homograft of either lymph node or skin from a black or white rat, its serum acquires the property of producing an abnormal degree of lymphocytopenia when injected into the donor of the graft." From this they conclude that homotransplants of normal tissues produce circulating antibodies in the serum of the hosts. But it is possible that this reaction is merely one of stress; the experiments would require repeating on adrenalectomized rats.

Demonstrable Antibodies to Transplantable Tumours

There have been a few reports from various sources claiming to have demonstrated antibodies to certain tumours. Kidd (1946) has demonstrated a specific antibody to the Brown-Pearce tumour; Gorer (1947) has been able to demonstrate three types of antibody to tumour inoculation in mice; Lumsden (1938) reported that he had found iso-haemagglutinins for certain tumours in the blood of the host; Cavelti and Cavelti (1945) claimed that, if kidney tissue mixed with bacteria is injected into rats, antibodies could be demonstrated; this latter work was not confirmed by Humphrey (1948).

It may be that, with proper techniques, antibodies to tissue antigens will be demonstrated in the serum of the host. However, as Medawar (1944) has pointed out, the general picture of immune reactions has been built up on antigen–antibody systems of great serological disparity so that "there is little likelihood that the homograft immune system, the most delicately differentiated of any that can be imagined, will fit into the bold and crude framework so defined."

But Gorer (1942b) has this to say: "The discovery that leukaemic cells may stimulate the production of iso-agglutinins would seem to indicate that the reactions cannot be separated from those generally studied by immunologists."

If there are no demonstrable antibodies in the serum of hosts after receiving homotransplants, where can we suggest they might be? The usual explanation is that as soon as the antibodies are formed they become cell-bound and so disappear from the serum of the host. This is not a convincing theory.

Tuberculin Hypersensitivity and Homotransplant Disintegration

Burnet and Fenner (1948) have postulated a similarity between tuberculin hypersensitivity and homotransplant disintegration: in neither case has antibody been demonstrated in the serum of hosts. These authors therefore conceived that "the immune reaction is not mediated by normal antibody, but by an agent of the type that has been postulated for the production of tuberculin hypersensitivity."

It seemed to us that if this were so, then total body irradiation of animals before tuberculin inoculation should delay the onset of a positive reaction. We have shown (Dempster *et al.*, 1950) that total body irradiation prolongs significantly the survival time of skin homotransplants in rabbits. It was decided to test the effect of irradiation on the development of tuberculin hypersensitivity. Our experiments show that parallel processes are not at work. It is true that total body irradiation will delay the development of a positive tuberculin reaction, but, once an animal has become positive, irradiation can temporarily abolish the established hypersensitivity; and, moreover, a positive reaction to further inoculation is delayed again. Craddock and Lawrence (1948) have shown that, in the case of bacteria other than the tubercle, when the antibody titre starts to rise irradiation has no effect in abolishing the titre; we have shown (Dempster *et al.*, 1950) a similar behaviour in the case of skin.

The development of tuberculin hypersensitivity and homotransplant disintegration are similar in that both can be delayed by irradiation before the first dose, but this seems to be as far as the parallel goes. Thus a concept of homotransplant disintegration must be sought of a nature different from the tuberculin hypersensitivity reaction.

Site of Antibody Production

The exact site of antibody production is still far from certain. The reticulo-endothelial system is concerned somehow; the lymphocytes and plasma cells, in particular, seem to play an active part. Fagraeus (1948) has suggested that the plasma cells are actually involved in the production of antibodies, and there is a considerable body of support for her concept. She regards the lymphocytes as transporters of already formed antibody. This theory is supported by a previous communication

by Bjorneboe and Gormsen (1943), who, after intense bacterial immunization of experimental animals, found marked enlargement of their spleens and plasma-cell proliferation of their spleens, livers, lungs, bone marrow, and adrenals; antibodies were not detected before the seventh day, though plasma cells appeared on the third. Similar results occurred with foreign serum protein inoculation. These workers hold that antibody production and plasma cell proliferation are parallel phenomena.

The relation between nutrition and antibody production was at one time thought to be of importance. Balch (1950), using diphtheria antitoxin, found no significant difference in antibody production in groups of well-nourished and poorly nourished humans. Neither did the antibody response appear to depend on age or serum protein levels.

Modification of the Homotransplant Reaction

Since the reticulo-endothelial system appears so intimately bound up with antibody production, attempts have been made to modify its reaction to a homotransplant. Such attempts fall into two main groups.

1. Methods Affecting the Transplant

(*a*) *Freezing.*—Blumenthal (1941) found this unproductive, but Casey and his co-workers (1948) reported what they describe as the XYZ phenomenon. They froze portions of the Brown-Pearce tumour for varying periods and then injected them subcutaneously in the form of an emulsion into rabbits known to be resistant; some 15 days later the fresh tumour was transplanted into the same rabbits with a high percentage of takes. This would appear to be a unique biological phenomenon; there is no record yet of its repetition.

(*b*) *Heating.*—Blumenthal (1941) reported that the host reaction is not elicited if the donor tissue is heated to a temperature of 54° to 56° C. This, however, is not surprising, as the donor tissue was probably not alive; only metabolizing cells can evoke an antibody response in an animal of the same species, though this does not seem to apply to heterologous transplants—that is, transplants from one species to another.

(*c*) *Immersion in Chemicals.*—Blumenthal (1941) found that if the homotransplant was immersed in certain chemicals for a number of hours the host reaction was inhibited; the presumption is that these cells, too, were dead.

(*d*) *Desensitizing.*—On the whole no success has been obtained by this procedure. Gaillard (1948), however, points out that, if cultured for 14 days in the blood plasma of the future host, parathyroids from stillborn babies take successfully. He reports favourably on 15 such transplants made for the treatment of post-operative tetany, but his criteria of survival were very indirect. It is difficult to assess the value of these observations.

All these methods are crude, and it is obvious that they cannot offer a profitable approach to the homotransplant problem: organs so delicate as the kidney, for example, would never survive such treatment.

2. Methods Affecting the Host

(*a*) *Mechanical Blockage of the Reticulo-endothelial System.*—Foulds (1932) and Ludford (1932) have reported success with tumour tissue using this method. Saphir and Appel (1943) have gone further; they report that daily intravenous exhibition of trypan blue in rabbits, rendered immune to the Brown-Pearce tumour, abrogate the immunity reaction in a certain proportion of animals.

(*b*) *Transplantation to the Brain and Anterior Chamber of the Eye.*—These areas provide a favourable nidus for homotransplanted tissue. It appears that homotransplanted tissue in such sites can respond to an immune reaction but is unable to evoke one. Medawar (1948) showed that homotransplanted skin will not grow in the forebrain of the rabbit if the latter has previously been specifically immunized against that particular skin. In addition, Medawar (1948) showed that "a skin homograft transplanted to the anterior chamber of the eye of a specifically immunized rabbit is destroyed if, and only if, it is penetrated by blood vessels." Woodruff and Woodruff (1950), however, report that thyroid grafts in the anterior chamber, even though they became vascularized, were not destroyed by any possible systemic reaction. No really satisfactory explanation of the successful growth of homotransplants in the above areas has been described so far.

(*c*) *Inhibition of the Activity of the Reticulo-endothelial System.*—The methods used have been these: dry heat, benzol, nitrogen mustards, total body irradiation, cortisone, and A.C.T.H. The last three of these have been used extensively in recent years and will be considered in more detail; the others will be ignored.

Effects of Total Body Irradiation on a Host's Reaction

A definite lowered resistance has been reported by many investigators when a host is irradiated before receiving a homotransplant. Murphy (1926) found a higher incidence of takes in an irradiated series of mice receiving homotransplanted tumours. Others have been able to transmit leukaemias in previously irradiated hosts (Krebs *et al.*, 1930; Furth *et al.*, 1933; Richter and MacDowell, 1935). There is also definite evidence that irradiation of the host will delay antibody formation in response to bacterial antigens (Murphy and Sturm, 1925; Craddock and Lawrence, 1948) and we have shown (Dempster *et al.*, 1950) that the survival time of homotransplanted skin of rabbits can be significantly prolonged by previously irradiating the hosts. The Birmingham workers (personal communication) have shown that cortisone will hold back the immunity reaction in skin homotransplants for a significant time.

These methods are, however, really only of value in elucidating the exact nature of the process of disintegration of the homotransplants. Cortisone and A.C.T.H. produce curious side-reactions, and so, except perhaps in the case of skin homografting, it would be inadvisable at this stage to contemplate any clinical use of them in homotransplant problems. Cortisone appears to have two distinct actions on the host: it delays healing, and it delays antibody formation for a time. The former action would in itself prolong the survival time of homotransplanted tissue, as delay in vascularization prevents full access of the antibodies to the tissue concerned. But it appears that at some time after the use of cortisone the host becomes refractory to the drug and the antibody-inhibiting effect of cortisone is lost. The irradiation methods have the disadvantage of lowering the general resistance of the animals and might be dangerous if used clinically, although Clemmensen and Andersen (1948) claim that if fractioned doses of irradiation are given instead of one large dose "it seems possible to prevent the development of immunity without serious damage to the general health of the animals."

Effect of Irradiation of Hosts Receiving Homotransplants of Skin

The effect of irradiating hosts before they receive skin homotransplants will be considered in greater detail, as certain important observations can be drawn from the results obtained. Figs. 11–14 show a natural history of the behaviour of homotransplanted skin on an

irradiated host. The survival time of the homotransplants has been significantly increased by total body irradiation; when only a local area was irradiated no increase in survival rate was observed. Irradiation after homotransplanting skin had no effect on the survival period of the skin homotransplants (Dempster *et al.*, 1950).

These results show that the antibody reaction to normal tissue parallels very closely indeed the antibody response to injected bacteria as demonstrated by Craddock and Lawrence (1948): these workers found that the antibody titre to injected bacteria was held back if the animals receiving these injections were previously irradiated; they also found, as we did in the case of skin, that irradiation of the animals after the bacterial injections had no effect on the antibody titre.

The other observation of more than theoretical interest is that total body irradiation, and to a less extent the administration of the cortisone drugs, by holding back antibodies in the host animals, permit homotransplanted skin to adapt itself to the host. This seems to me to introduce an element of hope that this vast and elusive problem might be solved by systematic attempts continued over many years. In the past, not unnaturally, there has been a profound pessimism. It was thought that complex metabolic processes were involved in addition to any possible immune reaction. Figs. 11–14 show that no support can be given to such extreme pessimism. On the other hand, the irradiation and the cortisone effect do demonstrate that even when homotransplanted tissue has taken and settled down satisfactorily in its new situation, no permanent adaptability develops: as soon as the antibody production began (when cortisone was withheld or with the development of a refractory state) the well-adapted homotransplanted skin died very quickly, and its fate was as decisive as if no delay in antibody production had occurred. Here, therefore, no support can be given to the postulate of Greene (1941): ". . . If for some reason the foreign body reaction is delayed and the transplant lives, it is conceivable that its cells may be gradually altered by the continued inhibition of host material so that some degree of adaptation results and the more radical constitutional differences between transplant and host are lost."

The Implication of the Theory of an Actively Acquired Immunity

Before proceeding further, let us consider the implication of Medawar's theory. His theory implies a humoral mechanism bringing about the disintegration of homotransplants which is supported by other evidence:

(1) The demonstration by Morgan Harris (1943) that the tissues of the rat and mouse can grow together, in harmony, in tissue culture: "In all cultures, adjacent rat and mouse fragments through cellular outgrowth eventually fused together to form a single structure, stable over culture periods ranging up to 36 days. . . . Fibroblasts, lymphocytes, and polymorphonuclear leucocytes of both species migrated out normally from explants, without any attraction toward the foreign cells present. No evidence of encapsulation or specific accumulation in the vicinity of alien elements was observed.

(2) The evidence of total body irradiation as against local irradiation (Dempster *et al.*, 1950).

(3) The cortisone effects described by the Birmingham workers.

(4) The parabiotic studies of Bichel and Holm-Jensen (1949) which show that, "if a rat has been made temporarily susceptible to transplantation of a mouse tumour by means of all-over irradiation with *x* rays, the parabiotic union of the animal with a non-irradiated partner will make this susceptibility disappear."

These observations, together with Medawar's own results, point strongly in favour of a humoral mechanism involved in homotransplant disintegration.

Transplantable Tumours

I have already referred to the fact that certain tumours are homotransplantable, and have quoted evidence that the laws of transplantation of neoplastic and normal tissues are essentially the same; they do, however, present certain differences in detail.

While it is almost certain that antibodies are produced in response to all transplanted tumours, yet on certain few occasions transplanted tumours grow in spite of an immune response on the part of the host; such tumours are referred to as transplantable tumours. Nearly all tumours disintegrate completely on being homotransplanted. While it is highly probable that cornea, cartilage, and blood vessels evoke some mild antibody response, the fact that these tissues are homotransplantable provides the only known normal tissue parallel to transplantable tumours.

Let us consider the explanation offered for the transplantability of tumours. Tumours, as a whole, possess a relatively high degree of adaptability. It has often been observed that transplantable tumours increase their growth momentum in each successive generation. These two facts are sometimes explained by the rapid cell multiplication and lack of cellular differentiation, but this explanation is not altogether convincing; most malignant tumours disintegrate rapidly when homotransplanted. It does not appear logical to accept, as an explanation of tumour transplantability, the general properties of malignant tumours as a whole. Another explanation of the transplantability of tumours is suggested by Gorer (1948), who has found evidence that tumours may undergo antigenic simplification during the course of serial transplantation. Other workers claim that transplantable tumours mutate during successive transplantation and suggest that this is the explanation of their transplantability. It must be concluded that this problem still remains obscure.

Craigie (1949) has stressed the importance of a quantitative approach to transplantable tumours. "So far as transplantable tumours are concerned I do not think that any real progress can be made with this problem until an adequate foundation of quantitative data has been laid down. It is necessary to determine, for example, using a representative series of selected tumours, the relationship between the dose of living tumour cells inoculated and the rate at which a tumour is produced at the site of an inoculation. It is also urgently necessary to discover to what extent tumour cells can survive under various environmental conditions *in vitro*. I believe that it is only against an adequate background of such knowledge that we can obtain evidence for or against the existence of carcinogenic viruses of low transmissibility to normal cells."

If, of course, a virus were operating in making certain tumours transplantable the problem of an actively acquired immunity would not arise with them.

Transplantability of Cornea and Blood Vessels

We may also ask why cornea and blood vessels are homotransplantable. Do these tissues not evoke an antibody response?

In the best of hands not all cornea homotransplants are successful; in fact, the success varies according to the selection of cases (Paufique *et al.*, 1948). If the cornea becomes vascularized, opacity is the result, and this constitutes a technical failure; but the vascularized cornea is not destroyed by an immune reaction. It would appear that corneal tissue placed correctly in position in front of the anterior chamber of the eye is incapable of evoking an immune reaction. The possible causes preventing the development of an immune reaction may be (1) the tissue is homotransplanted in such a low dosage as not to be effectively antigenic; or (2) the corneal tissue possesses very weak antigens or perhaps none at all. The only clinical report which might be interpreted as an immune reaction is the strange "maladie de greffe." This consists of sudden opacity, accompanied by vascularization, occurring some weeks after transplantation. It should be realized, therefore, that failures in corneal grafting are not due to an immunity reaction but to technical faults or other circumstances unrelated to an antigen–antibody reaction. The modern use of partial-thickness grafts is overcoming many technical difficulties.

Blood vessels, I believe, are not antigenic. If they are antigenic their specific antigens are not strong enough to evoke an immunity reaction of dimensions capable of effecting disintegration. Figs. 15–17 show sections of homotransplanted kidney, ureter, and reno-carotid anastomosis. This kidney has been homotransplanted to the neck of a dog; vascular anastomosis was effected by interposing the kidney on the carotido-jugular circulation of the host. Such a kidney secreted urine for three days before the dog suddenly developed the severe toxic state which has been described elsewhere (Dempster, 1950). It is obvious that the disintegrative process is well established in the kidney and ureter, but there is no sign of a cellular reaction in the renal artery. One would suppose that if the renal artery were antigenic some sign of cellular reaction would be visible. In addition, the reno-carotid anastomosis was healing at a time when neither kidney nor ureter showed any signs of adhering to the surrounding tissue planes of the neck of the host. The results of this experiment support the well-known clinical use of arterial homotransplants.

It will be convenient at this stage to clear up a misconception about the foetal aorta. There is a mistaken idea among some surgeons that the reason why the foetal aorta is homotransplantable is that, being embryonic tissue, it is non-antigenic. I have already referred to the exaggerated claims made for embryonic tissue. When referring to the antigenicity or non-antigenicity of embryonic tissue, it is absolutely important to state precisely the age of the embryo and the degree of morphological differentiation of the particular tissue: otherwise, statements that embryonic tissue is or is not antigenic are quite meaningless. The foetal aorta, however, is homotransplantable—not because it is embryonic tissue, but because blood vessels, embryonic or adult, do not appear capable of evoking an antibody response.

Kidney Homotransplantation

Over the last 40 years many attempts have been made to homotransplant kidneys in dogs and cats, but the time of survival of these transplants has been limited. Even with modern antibiotics the same position obtains. There is no doubt that some strange biological incompatibility is the cause of failure. A homotransplanted kidney in the dog will, however, maintain it in good health for some days before disintegration occurs. There is clear-cut evidence that, for as long as it functions, a homotransplanted kidney does so as well as an autotransplanted kidney. The autotransplanted kidney behaves in a very peculiar manner even when proved to have a remarkably normal microscopical architecture; it is unable to concentrate urine, and the reason for this is rather obscure. The autotransplanted kidney cannot reabsorb sodium and chloride efficiently, is unable to manufacture ammonia in normal amounts, and the titratable acidity of its urine is about one-third of normal. Exactly the same characteristics have been observed in the homotransplanted kidney while it is functioning. Histologically, autotransplanted kidneys removed after two months' functioning seem remarkably normal.

Lawler and his co-workers (1950) have recently reported a successful kidney homotransplant in a human female. The kidney apparently is still functioning after some five months. This achievement does not necessarily contradict all the previous experimental evidence. The lengths of survival of homotransplanted tissues may vary from species to species—for example, skin homotransplants survive about 10 days in the rabbit compared with about six weeks in the human. All the same, homotransplanted skin in the human almost always has a rather sickly appearance. Lawler and his co-workers claim that their success was due to accurate blood grouping, including Rh-negative type. But complete identity of blood group is extremely difficult to obtain, and so their success cannot lightly be attributed to this one factor alone. While this clinical experiment was a very courageous effort, it should be pointed out that an alarming toxic state develops in dogs receiving homotransplanted kidneys (Dempster, 1950).

The process of disintegration in the homotransplanted kidney is rather interesting. Most investigators have reported a mixed round-cell infiltration around the small blood vessels and glomerular capsule. This cellular infiltration is the first visible change; in the early stages the tubules appear healthy (Fig. 15), as do the glomeruli. The infiltration progresses until complete disintegration of the renal parenchyma occurs, as seen in Fig. 1. In my own experiments this cellular infiltration coincides with a toxic state in the dog (Dempster, 1950).

How is one to interpret the cellular infiltration? Loeb would interpret the cellular reaction in terms of a purely local interaction between kidney and the host in which the lymphocytes and plasma cells react to "differentials" locally in the kidney substance.

It has already been pointed out that homotransplanted skin disintegrates without any significant mesenchymal cell reaction. Thus one is obliged to proceed with caution before coming to any conclusion about the mesenchymal cell reaction in the homotransplanted kidney. There are two other possible interpretations besides that of Loeb: (1) The infiltration may be a proliferation of already existing reticulo-endothelial cells in the kidney. It is remarkable that the reticulo-endothelial system is most highly developed around the small blood vessels and glomerular capsules. It is exactly in these areas that the infiltrating round cells are first visible. This interpretation suggests that the homotransplanted kidney reacts against its host. (2) It is possible that the actual immune reaction in the homotransplanted kidney is an acellular one. But the effects of the immune reaction alter in some way the vitality of the homotransplanted kidney, and this change attracts the mesenchymal cells of the host.

Adrenal Homotransplantation

The adrenal has been reported to have been successfully homotransplanted in humans. The work of Broster and Gardiner-Hill (1946) in claiming successful cure of one case of Addison's disease is rather difficult to interpret in terms of the general theory of homotransplantation failure. It would be of great interest if biopsy specimens removed some considerable time after homotransplantation did, in fact, show definite survival.

Halsted's Law

A rather obscure subdivision of the general laws of homotransplantation is Halsted's law. Halsted (1909) found that parathyroid autotransplants were successful only if there existed in the recipient a marked deficiency of parathormone. From this one observation he formulated the general law that an endocrine organ transplant is more likely to be successful if there exists in the host a deficiency of its particular secretion. Other workers reported similar results, but Turner (1938, 1939) argued that Halsted's law did not apply when endocrine tissue was transplanted to the anterior chamber of the eye, which, as previously stated, provides a favourable environment for any transplanted tissue. Woodruff and Woodruff (1950) had few successes with subcutaneous endocrine-tissue homotransplants whether there was or was not a deficiency of the relevant hormone in the host; their endocrine transplants to the anterior chamber of the eye were more successful, and seemed to conform to Halsted's law. They demonstrated also, on evidence previously submitted by Turner (1938), that it was not directly the deficiency of the hormone of the transplanted tissue which was the responsible factor for survival but the excessive secretion by the anterior pituitary of the tropic hormone concerned with the particular endocrine tissue of which the host had been deprived. This seemed clearly proved by, for example, the high proportion of thyroid homotransplants obtained by the injection of the thyroid-stimulating factor in a host whose own thyroid gland was left intact.

The Role of Autotransplants

A survey of the whole field of tissues likely to be of value in a homotransplanted state makes it clear that, besides the general problem of the immune reaction, each tissue must have its own laws, which require to be strictly observed before homotransplantation can be successful. It should be the task of experimental surgery, therefore, to discover first the laws of behaviour of each tissue in the autotransplanted state at least as fully as they have been elucidated in the case of skin. For instance, as has already been pointed out, the homotransplanted kidney is unable to concentrate urine over the period during which it continues to function; this same phenomenon occurs in the autotransplanted kidney and so far, after a great deal of research, the loss of the ability to concentrate urine has not been explained.

The Problem of Storage of Organs

If the immunological problems and other problems involved in procuring a normal functioning organ were solved our difficulties would be by no means over. There would still remain the problems of storage of organs. This presents many difficulties. While there is no difficulty in preserving skin and blood vessels in the frozen state, other organs, such as kidney, would require more delicate handling. It is possible that an organ-perfusion apparatus may turn out to be the only safe method of preserving delicate organs ready for homotransplantation at any given moment.

The Future

The problems underlying homotransplantation of tissue have been traced to a no-man's-land where genetics and immunology meet. The solution, if there is one, of the immunological problem lies in the hands of those serologists willing to work in such an obscure field. Gorer (1950, personal communication) has pointed out the possible approach which serologists might follow: "The possibility of suppressing the defensive reactions against homografts without damaging those directed against infection is not at present in sight. Therefore the chance of obtaining permanent homografts must remain very small. However, this does not settle the problem. We know from experiments with transplanted tissues in animals and from blood-transfusion reactions in man that antigens differ greatly in their potency in eliciting an immune response. Thus it is generally agreed that the Rhesus antigen 'D' is far more important clinically than 'C' or 'E.' If we could improve our techniques for the detection of iso-antibodies we could doubtless label the more potent antigens. If this were done we might be able to select donors giving grafts of longer persistence than those chosen by chance alone."

Clinically, the homotransplant problem is of vital importance and its solution is increasing in urgency. The problem is so obscure that the widest research co-operation between experimental surgeon, clinical surgeon, serologist, and geneticist will be required for its solution; yet it is so vital that an organization for the co-ordination of these specialists, with the aim of achieving successful homotransplantation in man, would seem opportune.

Summary

An introductory statement stresses the clinical importance of solving the problem of tissue homotransplantation, and particularly that of skin.

A review has been presented of past theories of the nature of the disintegration of homotransplants—(*a*) the theory of athrepsia, (*b*) the theory of vascular deprivation, (*c*) the theory of natural immunity, and (*d*) the theory of a local cellular reaction—with in each case the reasons for their rejection.

Medawar's theory of actively acquired immunity is discussed and the experimental method used to support it is described.

The antigen–gene relationship is reviewed briefly.

The site of antibody production is discussed together with the failure to demonstrate, in the host serum, antibodies to transplanted normal tissues.

The degree of similarity of behaviour of tissues and bacterial antigens and antibodies is discussed, and a distinction is made between the nature of tuberculin hypersensitivity and that of homotransplant disintegration.

Past attempts at modifying the process of disintegration are reviewed under two heads: (*a*) methods affecting the homotransplant itself, and (*b*) methods affecting the host.

The effect is demonstrated of total body irradiation in prolonging the survival of homotransplanted skin, and evidence is presented of a humoral mechanism involved in homotransplant disintegration.

The transplantability of tumours is compared with the transplantability of certain normal tissues.

Halsted's law relating to endocrine transplants is discussed.

The functions of a complex organ transplant may not all persist equally, at least they do not in the case of the kidney, even though by histological criteria survival has been perfect.

The problem of storage of tissues may demand an elaborate solution.

The future of the homotransplant problem appears to be in the hands of serologists.

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EFFECT OF LOCALLY APPLIED CORTISONE ACETATE ON SURVIVAL OF SKIN HOMOGRAFTS IN RABBITS

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It has already been shown (Billingham, Krohn, and Medawar, 1951) that the daily systemic administration by intramuscular injection of 10 mg. of cortisone acetate to rabbits prolongs threefold or fourfold the lifetime of skin grafts that have been transplanted to them from other rabbits. It will now be shown that the direct local application of no more than 5 mg. of cortisone acetate every third day to such homografts will at least double their expected survival time. This effect has been found to be a genuinely local one—it is not due merely to the absorption of cortisone into the circulation—but to be very much weaker in rabbits that have been made immune by an earlier grafting of skin from the same donor or by a concurrent grafting of skin to which cortisone has not been locally applied.

Cortisone is known to bring about a well-defined eosinopenia after absorption through the skin of adrenalectomized mice (Speirs, 1951) and to cause atrophic changes of the dermis after local application to the skin (Castor and Baker, 1950). The subconjunctival injection of quantities of cortisone far too small to have a significant systemic effect has been used with success in the treatment of inflammatory conditions of the eye (Koff, Rome, Kaspe, Commons, Button, and Starr, 1950; Jones and Meyer, 1950).

Methods

Save where some variant is specially mentioned, we have continued to use the scheme of experiments described in our earlier paper. Each test made use of three rabbits chosen for their genetic disparity; one served as a donor, and eight circular ear skin grafts 9 mm. in diameter were transplanted from it to each of the other two. The homografts were transplanted to a large rectangular raw area stripped down to the level of the panniculus carnosus on the skin of the chest, and were so arranged as to alternate in chessboard pattern with eight autografts cut from the ears of the respective recipients. One recipient acted as control, receiving either no treatment or an injection or local application of the aqueous vehicle (" control fluid ") in which the cortisone was suspended. (The cortisone acetate was provided from a generous gift made jointly to the Medical Research Council and the Nuffield Foundation by Merck and Co., Inc. The control fluid was a saline solution containing 1.5% benzyl alcohol and other unspecified suspending agents.)

The survival time of the homografts was estimated, as hitherto, by the histological analysis of biopsy specimens removed at three-day intervals over the period of breakdown: it represents the time at which the destruction of the foreign skin epithelium is *just* complete. (For

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reasons that will be explained later, a slightly modified scoring system was used in some of the tests comprising experiments 3 and 4.) We have continued to use three subsidiary quantitative measures of the action of cortisone: (*a*) the degree of contracture of the prepared recipient area, measured by expressing its area at the twelfth day post-operatively as a percentage of its area on the day of operation; (*b*) the inhibition of mitosis in the epithelium of autografts of six days' standing; and (*c*) alterations in the total and differential white blood cell counts.

The "mitotic frequency" recorded in the accompanying Tables represents the mean number of mitoses counted in each 1-mm. strip of superficial graft epithelium and in the epithelium of the follicles underlying it. We have no evidence to qualify our belief that the mitotic indolence of the epithelium of grafts transplanted to cortisone-treated animals is a secondary consequence of the diminution of their dermal blood supply.

Controls

The lifetime of homografts transplanted between genetically very dissimilar rabbits and in the dosage we have used lies very uniformly within the range seven to nine days. This is made clear by Table I, which brings together the results recorded in our earlier paper and elsewhere in the present paper. The selection of such genetically dissimilar animals has some disadvantages—for example, the immunity elicited by first-stage homografts causes them to break down so fast that the curtailed lifetime of homografts transplanted to pre-immunized rabbits tends to be concealed numerically; but it has the overriding advantage of making the test on the effect of cortisone as exacting as it can be.

TABLE I.—*Summary of Control Rabbits*

Donor	Recipient	Mitotic Frequency of Autografts (± St. Error)	Graft Bed Area, 12 Days After Operation (% of Original Area)	Homograft Survival Time (Days)
Co–4 ..	Co–5 M	10·6±0·6	49	7
Co–8 ..	Co–7 M	11·4±0·4	36	9
Co–11 ..	Co–10 F	5·2±0·2	61	7
Co–14 ..	Co–13 M	4·6±0·4	37	7
Co–15 ..	Co–17 M	Not done	44	9
Co–18 ..	Co–20 M	Not done	44	7
Co–23 ..	Co–25 M	4·4±0·3	51	8
Co–26 ..	Co–28 F	9·2±0·5	52	14*
Co–30 ..	Co–31 F	5·8±0·3	51	8
Co–33 ..	Co–34 F	7·8±0·3	42	8
Co–35 ..	Co–38 M	6·6±0·4	31	6
Co–39 ..	Co–42 M	4·4±0·3	36	7
Co–50 ..	Co–52 F	8·8±0·6	41	9
Co–53 ..	Co–54 F	3·9±0·2	52	8
Co–62 ..	Co–64 M	11·9±0·6	48	7
Co–65 ..	Co–67 M	4·2±0·2	48	7

* See text for notes on animal Co–28.

Table I contains one conspicuously anomalous result—the homografts transplanted to Co–28 lasted half as long again as on any other control rabbit, and twice as long as on many. Co–28 was the only pregnant rabbit used in our experiments, and it delivered a litter of four normal young on the thirteenth day after operation. Since cortisone prolongs the life of foreign homologous tissue and is thought to be secreted in increased amounts during pregnancy, some increase in survival time of homografts might be expected. This has raised in our minds the possibility that an increased production of cortisone-like adrenal steroids during pregnancy may protect the mother against iso-immunization by the foreign homologous tissue of its foetus. The idea that there is a peculiar connexion between the activity of the adrenal cortex and the mammalian mode of gestation is not a new one (cf. Elliott and Tuckett, 1906).

The mitotic frequencies of six-day autograft epithelium are clearly very variable; they are distributed, markedly askew, about a modal frequency class of 4–6 and a mean of 7.1 mitoses per mm. Although the range of variation is great, the mitotic frequencies of six-day autografts on many cortisone-treated rabbits fall well below the lowest of them.

The areas of the general graft bed at the twelfth day post-operatively are distributed more or less symmetrically about a mean of 45% of the area of the general graft bed on the day of operation, with a standard deviation of 7.8. An area lying outside the range 30–60% would be expected to turn up by luck of sampling not more often than once in 20 trials.

Experiment 1: Effect of Locally Applied Cortisone

This experiment comprises the four independent tests summarized in Table II. The entries relating to the cortisone-treated animals are in italics and to their controls in roman type.

The first local application of cortisone was made by spreading 5 mg. of cortisone acetate in 0.2 ml. of suspending fluid with a glass rod over the general graft bed, after which the eight homografts and eight autografts were laid upon it. (Animal Co–32 received only 2.5 mg. of cortisone throughout.) Dusting the area with sterile sulphadiazine powder helped to secure an even distribution of cortisone by taking up some of the excess suspending fluid. The usual dressings, including an ordinary fine-meshed tulle gras, were always used. The animals were inspected and re-dressed every third day, when a further dose of 5 mg. (or 2.5 mg.) of cortisone was spread over the operation field and, of necessity, *over* the healed grafts. Applications were continued until the homografts had finally broken down.

The control recipients were treated in exactly the same way except for the substitution of 0.2 ml. of control fluid for the cortisone.

TABLE II.—*Effect of the Local Administration of 5 mg. of Cortisone Acetate Every Third Day (Co–32: 2.5 mg.). The Results Relating to Cortisone-treated Animals are Italicized.*

Donor	Recipient	Mitotic Frequency of Autografts (± St. Error)	Graft Bed Area, 12 Days After Operation (% of Original Area)	Homograft Survival Time (Days)
Co–30 ..	*Co–29 F*	*1·1 ± 0·2*	*72*	*>18 <21*
	Co–31 F	5·8 ± 0·3	51	8
Co–33 ..	*Co–32 F*	*0·4 ± 0·1*	*51*	*16*
	Co–34 F	7·8 ± 0·3	42	8
Co–50 ..	*Co–51 F*	*5·5 ± 0·5*	*68*	*>18 <21*
	Co–52 F	8·8 ± 0·6	41	9
Co–53 ..	*Co–55 F*	*2·9 ± 0·2*	*81*	*>18 <21*
	Co–54 F	3·9 ± 0·2	52	8

The local application of cortisone depressed the proliferative activity of the autografts (Table II, column 3), retarded the contraction of the general graft bed (column 4), and at least doubled the lifetime of the homografts (column 5). So much the Table makes clear. In addition, the local application of cortisone strongly inhibited the building up of granulation tissue, weakened the primary healing of the grafts, and retarded the outgrowth of epithelium over the general graft bed. (We again observed, however, that fibroblastic proliferation and the laying down of young fibrous tissue started promptly *under* such epithelium as had

grown outwards from the grafts, although the rest of the raw area, still unsurfaced, failed to build up granulations.) In all these respects the local application of cortisone had the same consequences as the systemic. The autograft donor sites on the ears, however, failed to give evidence of the systemic action of such cortisone as may have been absorbed through its area of local application; as in the control animals, they quickly became puckered and scabbed, and formed nobbly fibrous scars. Nor did the white blood cell picture deviate significantly from normal.

Experiment 2: Application of the Same Dosage of Cortisone Systemically

It will now be shown that the dosage of cortisone which prolongs the life of homografts when applied to them directly is almost wholly ineffective when allowed to reach the grafts only via the systemic circulation, after absorption from subcutaneous injections or from another prepared raw area.

In tests 1 and 2, symmetrically disposed raw areas were cut from *both* sides of the chest; eight homografts and four autografts were transplanted to one area, and 5 mg. of cortisone was applied every third day to the other. In tests 3 and 4, 5 mg. of cortisone was injected every third day under the skin of the thigh.

TABLE III.—*Effect of the Administration of 5 mg. of Cortisone Every Third Day, Either to a Contralateral Raw Area (Tests 1, 2) or Subcutaneously (Tests 3, 4). The Results Relating to Cortisone-treated Animals are Italicized. Controls Received Applications or Injections of 0.2 ml. of Control Fluid*

Test	Donor	Recipient	Mitotic Frequency of Autografts (± St. Error)	Graft Bed Area, 12 Days After Operation. (% of Original Area)	Homograft Survival Time (Days)
1	Co–35	*Co–36 M*	*2·9 ± 0·1*	*37**	*7*
		Co–38 M	6·6 ± 0·4	31	6
2	Co–39	*Co–40 M*	*1·1 ± 0·2*	*39**	*9*
		Co–42 M	4·4 ± 0·3	36	7
3	Co–62	*Co–63 M*	*3·8 ± 0·1*	*41*	*12*
		Co–64 M	11·9 ± 0·6	38	7
4	Co–65	*Co–66 M*	*1·4 ± 0·2*	*56*	*8*
		Co–67 M	4·2 ± 0·2	48	7

* The figures refer to the graft-bearing area—i.e., the one which did not receive cortisone.

The results are summarized by Table III. Comparison of the italicized entries (cortisone-treated animals) with the others show that the systemic or indirect application of 5 mg. of cortisone every third day has had very little effect on the life of the homografts or on the area of the graft bed on the twelfth day after operation. In all four trials, however, the homografts on the cortisone-treated animals outlived their controls, while the raw areas of animals given cortisone contralaterally were also less contracted. Such a result would be reproduced by luck not more often than once in every sixteen such sets of trials, and provides weak evidence that the cortisone had some slight effect. It will also be seen that the cell-division frequency (column 4) in six-day autografts was significantly lower in the cortisone-treated animals than in their controls. Since the white blood cell count revealed no such well-defined difference, the mitotic count appears to be the more sensitive indication of the action of cortisone.

In spite of these minor reservations, comparison of Table II with Table III shows quite clearly that the prolongation of the life of homografts by the local application of cortisone does not depend on the absorption of cortisone into the systemic circulation. The results of later experiments fully confirm this judgment.

Experiment 3: Cortisone Locally Applied to Homografts on Specifically Pre-immunized Rabbits

Four control animals (Co–31 and Co–34 from experiment 1, Table II; Co–38 and Co–42 from experiment 2, Table III) were now made the subjects of second-stage operations. Fifteen or seventeen days after their first operation—that is, about a week after the homografts transplanted upon that occasion had finally broken down—eight homografts were again taken from each of their respective donors. Symmetrically disposed raw areas were then cut from both sides of the chest of each recipient and four homografts were transplanted to each side. Cortisone (5 mg. in 0.2 ml. of control fluid) was applied every third day to one of the graft-bearing areas, and 0.2 ml. of control fluid to the other.

The practice of subdividing the homografts into two sets at the second-stage operation and applying cortisone to only one of them made it possible to compare the survival time of cortisone-treated second-stage grafts (the italicized entries of columns 6 and 7, Table IV) not only with that of the first-stage grafts from the same donor (column 3) but also with that of their untreated second-stage contemporaries on the other side of the chest (entries in roman type, columns 6 and 7). This operative procedure is not objectionable on immunological grounds, because the recipients were (and were intended to be) highly immunized, and the untreated second-stage grafts could only have reinforced the immune state already in being.

TABLE IV.—*Effect of Locally Applied Cortisone (Italicized Entries) on the Lifetime of Homografts Transplanted to Pre-immunized Rabbits. Each Recipient Bore Four Homografts on Each Side of the Chest; 5 mg. of Cortisone was Applied Every Third Day to One Side Only*

Donor	Recipient	1st-stage Survival Time (Days)	Day of 2nd-stage Operation	Side	2nd-stage Survival Time (Days)	90% Breakdown Time (Days)
Co–30	Co–31 F	8	17th	*Right*	*>9 <12*	*>6 <9*
				Left	<6	<6
Co–33	Co–34 F	8	17th	*Right*	*15*	*>12 <15*
				Left	7	7
Co–35	Co–38 M	6	15th	*Left*	*8*	*>6 <9*
				Right	<6	<6
Co–39	Co–42 M	7	15th	*Right*	*15*	*9*
				Left	7	7

The results summarized by Table IV show that the local application of cortisone to grafts on specifically immunized rabbits has much the same degree of effect as the systemic administration of 10 mg. per day, described in our earlier paper (Billingham *et al.*, 1951). It also has the same kind of effect on the histological appearances of the grafts.

Taken at their face value, the numerical results entered in column 6 indicate that cortisone brings about a very well defined prolongation of survival. Unfortunately, the bald numerical results are misleading. Breakdown had *started* in the cortisone-treated grafts of three animals by the sixth day and was far advanced by the ninth day in all four of them. There was no epithelial outgrowth from any of the homografts. The grafts were flat and diaphanous, and looked quite dead from the ninth day onwards. The graft vessels broke down and their lumina disappeared, leaving the grafts as thin avascular collagenous pads which

could be peeled away from their beds without bleeding. Yet, in spite of these disabilities, the homograft epithelium on three animals survived for many days as a thin, wholly indolent surface film one or two cells thick. The epithelial cells showed the ischaemic changes (swelling and neutrophilic reaction of the cytoplasm and chronically incipient nuclear pyknosis) often to be seen in unvascularized skin grafts lying in the anterior chamber of the eye (Medawar, 1948a) or in skin cultivated *in vitro* under a gas phase insufficiently rich in oxygen (Medawar, 1948b).

To discount this confusing effect, the entries in the last column of Table IV have been computed for a 90% breakdown time instead of for a 100% breakdown time. This minor adjustment of scoring does not influence the estimates of survival for the homografts on the control sides, because their breakdown was both quicker and regularly progressive. (The precocious breakdown of graft vessels and the survival of the epithelium, for as long as it does survive, in a wholly indolent or vegetative state, is the rule in ordinary untreated second-stage homografts; cortisone treatment makes the breakdown a more long-drawn-out process.)

From this supplementary evidence, which the numerical estimates for survival time do not bring to light, it may be argued that locally applied cortisone does *not* prolong the life of homografts on specifically preimmunized animals either in the same way or to anything like the same degree as it prolongs their life on "virgin" animals. That it has *some* slight local effect on such grafts is made clear by comparing the entries for the left-hand and right-hand sides of the body. These conclusions are reinforced by the results of experiment 4.

Experiment 4: Cortisone Locally Applied to Homografts on Animals Undergoing Independent Concomitant Immunization

In the experiments described in the preceding section cortisone was locally applied to homografts on animals that had been specifically immunized before the grafts were transplanted to them. It now appeared to us important to examine the effect of cortisone locally applied to homografts on "virgin" animals but subjected to a vigorous *concomitant* immunization. In effect, this simply entailed preparing *two* raw areas on a hitherto untreated animal, transplanting homografts to both of them but applying cortisone to only one. This procedure differs in several qualitative ways from that in which homografts are transplanted to preimmunized animals, one of the most important being that the cortisone-treated grafts have time to acquire a functionally adequate blood supply before being overwhelmed by the immunity reaction provoked by their untreated contemporaries.

If our general interpretation is correct—that cortisone acts mainly by retarding the development of an immune state rather than by preventing its local fulfilment in the grafts—then (*a*) the cortisone-treated grafts of this experiment should have much shorter lives than those of experiment 1, in which cortisone was applied to *all* the grafts borne by their recipients; and (*b*), a corollary of (*a*), the difference between the survival times of the homografts on the treated and untreated areas should be small, and in any event much smaller than the differences revealed by the experimental and control animals of experiment 1. (As with experiment 3, however, such differences as there are must reveal the effect of cortisone in preventing the local expression of the immune state.) The results of the eight tests summarized by Table V show that these expectations were fulfilled.

The eight tests that comprise experiment 4 were subdivided into two groups of four, according to whether the two raw areas prepared on each animal lay one on each side of the chest ("bilateral operations") or both on one side of the chest ("unilateral operations"). The intention was that the two sets of homografts should have, in the bilateral operation, a completely separate lymphatic drainage, and in the unilateral operation a common drainage. It seemed to us a reasonable guess that the draining lymph nodes play an important part in the building up of immunity against homografts and that cortisone, when locally applied, may act in some degree by incapacitating the draining nodes. If both these guesses were true, the untreated homografts of the unilateral operation should live as long as the cortisone-treated grafts; both sets should live as long, or almost as long, as homografts do when *all* are treated with cortisone, as in experiment 1; and both sets should outlive the homografts of the animals operated upon bilaterally. Since Table V shows that these expectations were not fulfilled, the subdivision into bilateral and unilateral operations may be disregarded.

In practice, as Table V shows, the animals operated upon bilaterally and unilaterally were paired by a common donor. Sixteen grafts were taken from the donor and four grafted to each area on each recipient. The bilateral raw areas were symmetrically disposed on each side of the chest; the unilateral raw areas were rectangles of the same size, elongated dorso-ventrally, and lying symmetrically about the lateral thoracic vessel group. The two unilateral areas were separated from each other by a "vaselined" wall of normal skin not less than 1 cm. wide; cortisone was always applied to the homografts on the anterior area. The dosage of cortisone was the same for all animals—5 mg. applied locally

TABLE V.—*Effect of Cortisone Applied Locally to Only One of Two Separate Sets of Homografts Carried by Each Recipient (Italicized Entries). Co–61 Died on the Ninth Day after Operation. The Survival Times of the Homografts from Donors Co–44 and Co–47 were Computed on a "90% Breakdown" Basis*

Bilateral Operations					Unilateral Operations			
Donor	Recipient	Side	Graft Bed Area 12 Days After Operation. (% of Original Area)	Homograft Survival Time (Days)	Recipient	Area	Graft Bed Area 12 Days After Operation. (% of Original Area)	Homograft Survival Time (Days)
Co–44	Co–45 F	*Right*	*80*	*>15 <18*	Co–46 F	*Anterior*	*72*	*>12 <15*
		Left	54	9		Posterior	68	12
Co–47	Co–48 F	*Right*	*61*	*12*	Co–49 F	*Anterior*	*46*	*12*
		Left	48	10		Posterior	39	11
Co–56	Co–57 M	*Left*	*61*	*10*	Co–58 M	*Anterior*	*66*	*13*
		Right	34	8		Posterior	38	12
Co–59	Co–60 M	*Left*	*62*	*10*	Co–61 M	*Anterior*	—	*9*
		Right	38	9		Posterior	—	7

every third day. The areas not treated with cortisone received applications of 0.2 ml. of "control fluid" every third day.

The entries in Table V that relate to cortisone-treated areas are italicized. For the reason explained in the description of experiment 3, it was necessary to score the homograft survival times in the first two tests (donors Co–44 and Co–47) on a "90% breakdown" basis. Disregarding the subdivision into unilateral and bilateral operations, we find (*a*) that locally applied cortisone is as little able to protect homografts against a concomitantly developed immunity as against a pre-existing immune state (experiment 3); and (*b*) that locally applied cortisone does prolong the lifetime of homografts to some small degree even against a vigorous concomitant immunity, for the eight sets of locally treated homografts outlived their respective controls on every occasion. Since the immune state is systemic, the difference revealed by comparison (*b*) must be the consequence of cortisone's inhibiting the local expression of the immune state. This experiment, like its predecessor, thus makes it possible to distinguish between the effects of cortisone in preventing the development of an immune state and in preventing its local fulfilment. The former effect greatly outweighs the latter.

The homografts on the untreated areas of animals Co–46, Co–48, Co–49, and Co–58 survived a little longer than ordinary control homografts. This may well have been due to the very weak systemic effect brought about by the absorption of cortisone through its area of local application (see experiment 2). The prolongation of survival is more prominent in the control homografts of the unilateral series, but this is not acceptable evidence of the validity of the hypotheses upon which the subdivision into bilateral and unilateral operations was based (see above).

Discussion

Our results show that the life of homografts on rabbits can be prolonged by the local application of cortisone acetate. As it turned out, the local administration of 5 mg. every third day was somewhat less effective than the systemic administration of 10 mg. every day. It is likely that the local application of smaller quantities at more frequent intervals would have been more effective; and it is possible that cortisone can be better applied than as crystals suspended in a watery base, though the work of Speirs (1951) shows how quickly cortisone is absorbed, even through intact skin, when applied in an ointment base.

The results confirm our earlier interpretation that cortisone acts predominantly by retarding the systemic development of immunity to homografts rather than by preventing its local fulfilment in the grafts. (Its effect upon the "homograft reaction" is in this respect closely analogous to its effect upon the development and local expression of the Arthus reaction in rabbits: Germuth and Ottinger, 1950; and cf. also Harris and Harris, 1950.) This generalization is as valid for homografts transplanted to pre-immunized animals (experiment 3) as for homografts under concomitant immunization (experiment 4). Cortisone does, however, prevent the local expression of the immunity reaction in some small and discernible degree, for, no matter how the immunity had been provoked, the cortisone-treated grafts invariably outlived the untreated homografts borne by the same recipients (experiments 3 and 4). Cortisone may be acting in different ways to bring about these two distinguishable effects: the very slight prolongation of the life of homografts on concomitantly immunized or pre-immunized animals might be the consequence of an antihistaminic action, an alteration of vascular permeability, or an indirect effect on the division rate of epidermal cells. Whatever its mechanism, this relatively unimportant component of the action of cortisone is better achieved by local application than by systemic administration, for the breakdown of foreign cells in a homograft is accompanied by the congestion and disruption of its blood supply, and, if cortisone has been applied systemically, failure of the blood supply must obviously deny cortisone access to the graft.

The chief clinical advantage of applying cortisone locally is, of course, that it can be used in quantities that do not produce an unwelcome systemic effect. The local dosage of cortisone that doubles the life of homografts has, indeed, a trivial systemic effect. But the results of experiment 4—in which cortisone was applied locally to only one-half of the population of homografts, instead of, as in experiment 1, to them all—enforce one important precaution upon its clinical use: cortisone must be applied locally to *all* the foreign skin transplanted to a patient. This requirement may not always be at all easy to fulfil.

Summary

Skin homografts transplanted in a stated fixed dosage between rabbits of high genetic diversity survive their transplantation for six to nine days.

The local application of 5 mg. of cortisone to such homografts every third day at least doubles their survival time.

The dosage of cortisone that is effective when applied locally is ineffective when administered systemically.

The local application of cortisone to homografts is almost wholly ineffective when they are transplanted to a rabbit pre-immunized by an earlier grafting of skin from the same donor or concomitantly immunized by untreated homografts transplanted on the same occasion.

The principal action of cortisone on homografts is to retard the development of immunity towards them. Cortisone also has a slight but discernible effect in preventing the local expression of the immune state.

If cortisone is to be used by local application to homografts in clinical practice it must be applied to *all* the homografts transplanted to any one patient.

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Writing in the October issue of *Aeronautics*, the chief medical officer of British European Airways remarks that "indigestion and haemorrhoids are so common among aircrew that they may well come to be regarded as occupational ailments."

TRANSIENT DISTURBANCES OF CONSCIOUSNESS IN HEPATIC CIRRHOSIS

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The occurrence, in hepatic cirrhosis, of transient disturbances of consciousness which cannot be related to cholaemia was mentioned by Osler in 1892. Himsworth (1947) states: "Coma is peculiar in possessing no striking features. The patient seems quietly asleep—limbs have a peculiar 'clasp-knife' rigidity, not unlike that in Parkinson's syndrome, and the plantar reflexes are extensor . . . the majority then quietly die, but recovery sometimes occurs even at this stage." Otherwise this syndrome has received scant attention in the medical literature, and it was thought that it might be of value to revive interest in the condition by publishing a brief account of three such cases.

Case 1

A married woman aged 48 was admitted on April 19, 1947. She gave a history of long-standing jaundice and of swelling of the abdomen and ankles, exertional dyspnoea, and intermittent painless diarrhoea for three years. For six months she had been having attacks of unconsciousness, usually lasting about 24 hours. They came on without warning, usually when she was in bed. Between attacks she felt quite normal apart from her diarrhoea, diminished exercise tolerance, ascites, and leg oedema. There was nothing relevant in her previous health, family history, or social background.

Physical examination revealed slight icterus, multiple spider naevi on the face and trunk, and moderate oedema. There was considerable ascites; the liver was palpable, hard, and irregular but not appreciably enlarged; and the spleen could also be felt (grade I). The chest was normal clinically and radiologically (except for a high diaphragm) and there was no cardiovascular abnormality. The urine was free from albumin and sugar, and examination of the central nervous system revealed no abnormal physical signs. A "barium swallow" demonstrated the presence of oesophageal varices. Liver-function tests showed a reversed albumin–globulin ratio (serum albumin 2.4 g.%, serum globulin 3.8 g.%), a high serum alkaline phosphatase (23.7 units, Jenner and Kay), a positive direct and indirect van den Bergh reaction (serum bilirubin 2.5 mg. per 100 ml.), a five-plus cephalin-cholesterol reaction, a thymol turbidity of 5 units, and a colloidal gold of 44310. The blood count showed a slight macrocytic anaemia with 3,860,000 red cells, 82% (11.3 g.%) haemoglobin, 3,600 white cells, and a normal differential distribution. A fat balance showed 81% absorption. Abdominal paracentesis produced a straw-coloured fluid with a specific gravity of 1025 and a protein content of 880 mg. per 100 ml.

Whilst in hospital the patient was afebrile and the ascites and leg oedema subsided. There was, however, considerable diarrhoea, and three attacks of "unconsciousness" occurred. Each lasted about 24 hours, and, though the patient was stuporous, consciousness was not completely lost. In one attack she got out of bed and passed urine on the floor. During the attacks no abnormality could be found on examination of the cardiovascular or central nervous systems, and between the attacks she was mentally alert and normal. Blood-sugar estimations during the attacks were within the normal range, and a glucose-tolerance test was completely normal. An *x*-ray film of the skull was normal, but electro-encephalography carried out during two of the episodes of coma showed grossly abnormal records with a continuous dominant rhythm of 3–6 cycles a second and phase reversal at the parietal and temporal electrodes on both sides. She was discharged at the end of May, 1947.

The patient was readmitted in October, 1947, when her physical condition and liver-function tests had not materially altered. She continued to have attacks of unconsciousness, and ultimately died in Warwick Hospital on February 25, 1948.

Necropsy confirmed the presence of gross multilobular hepatic cirrhosis with splenomegaly and oesophageal varices. The stomach contained blood, there was haemorrhage into the liver substance, and a large haemorrhage from the left middle cerebral artery had destroyed the greater part of the left cerebral hemisphere.

Case 2

A married woman aged 66 was first seen on October 17, 1950. She gave a history of a lifelong tendency to bouts of diarrhoea, and of intermittent soreness of the tongue for many years. In 1940–1 she had been investigated at the Lincoln County Hospital because of abdominal pain and vomiting. A barium meal, cholecystography, and intravenous pyelography at that time showed no abnormality, but gastric analysis revealed achlorhydria.

She was again admitted to Lincoln County Hospital in 1945, when her liver and spleen were both enlarged three fingerbreadths below the costal margin, her blood pressure was raised (175/100), and her heart slightly enlarged both clinically and radiologically. A barium meal and an intravenous pyelogram again showed no evidence of disease. A blood count was normal, and a fractional test meal on this occasion was within the normal range. When first seen her chief complaint was of pain in the left side of the abdomen. There was a generalized brownish discoloration of the skin, the liver was a little enlarged and hard, and the spleen could also be felt (grade I). Her heart was enlarged to the left, her blood pressure was 220/130, and there were frequent extrasystoles. The urine was free from albumin and sugar and the chest was clear. Examination of the central nervous system revealed no abnormal physical signs. She had recently developed attacks of unconsciousness lasting for hours or days. In one of these her doctor diagnosed a "stroke," but there were no neurological abnormalities. She recovered from this and all her other attacks spontaneously and was quite normal, carrying out her full household duties during the intervals between attacks.

She was next seen on January 12, 1951, when she was completely unconscious, febrile (temperature 102° F.—38.9° C.), and grossly oedematous, with ascites and a right pleural effusion. She recovered consciousness and her mental state was normal, but her oedema and ascites increased, her pleural effusions became bilateral, and jaundice developed. She was transferred to this hospital on February 5, and, though bright, alert, and communicative on admission, the following day she became drowsy and incontinent, could be roused only by painful stimuli, and had to be fed through a Ryle's tube. She had recovered completely by the next day, but then again became stuporous for 48 hours, and after one more day of comparative normality gradually lapsed into coma with increasing oedema and jaundice and died on February 20.

During all the observed phases of unconsciousness no change in the cardiovascular state could be detected, and there were no abnormal neurological signs. Electrocardiography between and during attacks was normal apart from a left preponderance, a skull *x*-ray film was normal, and lumbar puncture showed normal hydrodynamics, chemistry, and cytology. The fasting blood sugar was normal, and during an attack it was 164 mg. per 100 ml. The serum sodium, potassium, calcium, phosphorus, and chlorides and the blood *p*H were all within the normal range, and the blood urea was 44 mg. per 100 ml. The Wassermann reaction was negative in the blood and cerebrospinal fluid.

Electroencephalography carried out during two of the periods of coma showed grossly abnormal records, with high-voltage delta discharges in all leads and phase reversal in the temporal lobes on both sides. Throughout the records there were periods of low-voltage fast activity and also runs of 9 cycles a second alpha rhythm.

Liver-function tests showed a reversed albumin/globulin ratio (serum albumin 2.39 g.%, serum globulin 3.1 g.%), a high serum alkaline phosphatase (19.5 units, Jenner and Kay), a positive direct and indirect van den Bergh (serum bilirubin 5.4 mg. per 100 ml.), a four-plus cephalin-cholesterol reaction, a thymol turbidity of 7 units, and a colloidal gold of 55321. The blood showed an incipient macrocytic anaemia with 4,370,000 red cells, 96% haemoglobin, and a mean corpuscular volume of 102.9 μ^3. The total white cell count was 11,800, 87% of which were polymorphonuclears.

Necropsy confirmed the presence of gross atrophic multilobular cirrhosis of the liver, the whole organ weighing 700 g. The portal vein was dilated, thickened, and atheromatous; the spleen was enlarged (345 g.), with numerous adhesions around it; while the oesophagus showed varices extending up to the bifurcation of the trachea. A suppurative cholecystitis and a solitary gall-stone, the presence of which had not been suspected during life, were also found. The heart showed moderate left ventricular hypertrophy. The brain appeared normal except for a depressed scar on the upper surface of the left cerebral hemisphere in the region of the post-Rolandic gyrus. In particular, the basal ganglia showed no macroscopic abnormality and the cerebral arteries were strikingly free from atheroma. Histological examination of the cortex, basal ganglia, hypothalamus, mid-brain, pons, and medulla revealed nothing that could be regarded as abnormal in a patient of this age.

Case 3

An unmarried woman aged 20 gave a history of chorea when 8 and of never having menstruated. There was no history of any illness suggestive of infective hepatitis. When 16 she had a tonsillectomy for recurrent sore throat, and thereafter had bouts of diarrhoea, with loose pale frothy stools, accompanied by ankle oedema. The oedema was worse at the end of the day, particularly when the weather was hot, and subsided completely with rest. Some two years later she noticed that the oedema involved the face, the arms, and the abdomen, as well as the legs, and that when it was developing she was thirsty and when it was subsiding there was polyuria. The attacks, which lasted up to three weeks, seemed to follow upper respiratory tract infections, and the bowels moved up to 15 times daily during these episodes. She was investigated in two hospitals, and the only treatment found to be effective was mersalyl injections.

She was seen in January, 1951, and was admitted for investigation. Physical examination showed finger-clubbing, "liver palms," multiple spider naevi on the face and arms, and considerable acne. Otherwise there were no abnormalities; the secondary sex characteristics were normally developed, the liver and spleen could not be felt, there was no ascites, and the urinary cardiovascular and central nervous systems were normal. The chest was clear clinically and radiologically. The electrocardiogram was normal, and the blood Wassermann reaction was negative.

She remained in hospital for 10 weeks, and during this time the occurrence of coincident bouts of diarrhoea and water storage was confirmed. The stools were loose, pale, and frothy, and microscopically showed an excess of fatty-acid crystals. Repeated fat balances showed a fat absorption varying from 87% to 90%. Sigmoidoscopy was normal, but a barium enema showed a lack of colonic haustration, while a barium series showed a suggestion of oesophageal varices and irregular filling and a "snowstorm" effect in the jejunum. A glucose-tolerance test was normal. Repeated liver-function tests all showed evidence of hepatic dysfunction with a reversed albumin/globulin ratio (albumin 2–2.7 g.%, globulin 2.8–3.3 g.%), a cholesterol of 74–166 mg. per 100 ml., an alkaline phosphatase of 15.8–18.4 units (Jenner and Kay), and an invariably positive direct and indirect van den Berg reaction, with serum bilirubin levels of 1.3–3.1 mg. per 100 ml. The flocculation tests were always strongly positive—a four-plus cephalin-cholesterol reaction, a thymol turbidity of 4–6 units, and a colloidal gold of 44321 or higher being present on each occasion.

Needle biopsy of the liver revealed destruction of the liver parenchyma and replacement by granulation tissue, the liver cells showing vacuolation of the cytoplasm. The blood count while she was in hospital always showed evidence of a slightly macrocytic anaemia, with red cells from 3,260,000 to 3,890,000 and haemoglobin from 68 to 82%. The total and differential white cell count and the reticulocytes were always within the normal range, and the mean corpuscular volume varied from 86.6 to 102.5 μ^3. Hess's test was negative and the prothrombin was 53%.

The patient was regarded as suffering from hepatic cirrhosis, and the alimentary defects were thought to be secondary to this, though they may have been the primary cause of the liver disease, for which no other cause was evident. She was discharged from hospital on April 21, and shortly afterwards entered into a phase of water retention and diarrhoea lasting five days. Though this episode resolved in the usual way, she did not recover her normal health; her appetite was poor, she was depressed, irritable, and intolerant of noise, and at times restless and excitable. Her parents stated that she seemed tired and drowsy and often sat with a vacant stare, whilst at other times she seemed confused and disorientated and kept repeating phrases and questions. They also said that she slept badly, and they had noticed restlessness and jerking and twitching of the limbs at night. Epistaxis occurred on three or four occasions. On May 19 she again developed thirst, diarrhoea, and increasing oedema, and vomiting also occurred. Three days later she seemed very drowsy, and at 10 a.m. went to bed. During the day she became quite unconscious and was readmitted to this hospital on that evening.

On admission she was comatose but restless, and there were frequent jerky movements of the arms and legs, which exhibited clasp-knife rigidity. She was grossly oedematous, the liver and spleen were still impalpable, and liver dullness was absent. She remained in coma of varying depth for three days and then with the subsidence of oedema recovered full consciousness. During this attack she showed some pyrexia (up to 100.6° F.—38.1° C.), was incontinent, and had to be fed through a Ryle's tube. There were some athetotic movements and much twitching of the limbs, and she yawned frequently; her face was expressionless, and her speech slow and monotonous. For a few hours the right plantar response was extensor. During this phase of unconsciousness the blood urea, blood sugar, serum sodium, and serum potassium were all within the normal range, but the chlorides were high (407–413 mg. per 100 ml.), and the carbon dioxide combining power was only 40 volumes %. After recovery of consciousness, however, the chloride level was still approximately the same. Electroencephalography, carried out during the unconscious phase, showed a large

dominant slow rhythm in all leads, with phase reversal at both temporal electrodes, but when full consciousness was restored the electroencephalographic pattern reverted to normal.

She remained in hospital for 12 weeks, during which one further brief episode of thirst, diarrhoea, increased oedema, pyrexia, and drowsiness occurred, and throughout her stay intermittent twitchings of the feet were noticed. There were no other neurological abnormalities, and Mr. Jameson Evans reported no Kayser–Fleischer rings. Fat balances, liver-function tests, and haematological investigations were substantially the same as during her previous period in hospital except that her anaemia was more severe. After a large blood transfusion she was discharged to her home subjectively well, and so far no further episodes of unconsciousness have occurred.

Discussion

A relationship between hepatic cirrhosis and degenerative changes in the brain has been well recognized since Kinnier Wilson (1912) published his classic description of six cases of progressive lenticular degeneration in which hepatic cirrhosis was associated with symmetrical degeneration of the putamen, globus pallidus, and caudate nucleus evidenced in life by tremor, muscular rigidity, dysarthria, dysphagia, and emotionalism, and he pointed out the strong hereditary and familial bias in this condition. Hadfield (1923) described a similar case in which necropsy revealed degenerative changes in the cortex (particularly the frontal cortex) and the dentate nucleus as well as the basal ganglia. Greenfield, Poynton, and Walshe (1924) described a further case and pointed out that pseudosclerosis and torsion spasm were variants of the same condition. Barnes and Hurst (1925) recorded a family of eight, five of whom were afflicted with hepato-lenticular degeneration. Their necropsy findings confirmed that degenerative changes occur in the cortex and cerebellum as well as the basal ganglia.

Later, Scherer (1933), in a study of 41 patients dying from cirrhosis and other forms of liver disease, found evidence of degeneration in the brain in over 90%. This consisted of changes in the oligodendroglia and the occasional presence of Alzheimer cells, and showed no predilection for the basal ganglia.

Crandall and Weil (1933) produced liver atrophy in dogs and rats by common-bile-duct ligation. They found that degenerative changes rapidly supervened in the corpus striatum, cerebral cortex, mid-brain, and cerebellum.

Brouwer (1935–6), in a review of the relationship between liver disease and the brain, mentioned two cases of hepato-lenticular degeneration in which, in addition to the symmetrical lesions in the corpus striatum, the cerebral cortex, particularly in the frontal area, showed cavitation and gliosis. He also described a case of haemochromatosis in which there occurred attacks of mental confusion, restlessness, urinary incontinence, and somnolence lasting two or three days. Later, emotionalism, dysarthria, dysphagia, tremor, and ataxia developed, and a necropsy showed parenchymal degeneration with gliosis, cavitation, and Alzheimer cells in the corpus striatum and frontal cortex.

Rabiner, Joachim, and Freiman (1944) recorded two cases of hepato-lenticular degeneration in which splenectomy appeared to have aggravated the nervous symptoms and hastened the fatal issue.

The association of hepatic disease with degenerative changes in the brain therefore seems well established. In the first two cases here described there was, however, no evidence of any neurological abnormality during life, apart from the episodes of coma, and no structural change was found in the brain except the terminal cerebral haemorrhage in Case 1. No histological examination of the brain was made in this case, but in the second case the brain showed nothing that could be regarded as abnormal at the age of 66, either macroscopically or histologically. The third case, however, has shown objective evidence suggestive of striatal disturbance.

Though no precise explanation of the attacks of unconsciousness is offered, the third case does suggest that they may arise from factors similar to those which operate in Wilson's disease, and Brouwer's above-mentioned case of haemochromatosis supports this hypothesis.

Though the attacks, of themselves, do not appear to be in any way dangerous or to require any particular treatment, and though they cannot be regarded as cholaemic in the ordinary sense in which that term is used, their occurrence probably portends, like the development of ascites, a fatal termination within a period of months. Death occurred in the first case sixteen months and in the second only four months after the first attack of unconsciousness.

In each of the three cases ascites and oedema were present when the attacks occurred, and it is possible that fluid retention may in some way be responsible, though the second and third cases suggest that this is not related to sodium retention, as the serum sodium was within the normal range in both subjects. Certainly in each case there was abundant evidence of gross parenchymatous liver disease.

The electroencephalographic abnormalities observed during the periods of unconsciousness are probably non-specific and simply the result of coma, as the third case reverted to a normal electroencephalographic pattern between her episodes of unconsciousness.

Summary

Transient attacks of unconsciousness are described in three cases of hepatic cirrhosis.

Death in cholaemia followed within a period of months in two of the cases.

The attacks were associated with fluid retention, but the precise mechanism of their causation is not understood.

We are greatly indebted to Professor P. C. P. Cloake for the electroencephalographic studies, to Dr. A. P. Prior for the necropsy report on Case 1, to Professor J. M. Orr for the necropsy and histology of Case 2, to Dr. J. V. S. A. Davies for details of the previous history of Case 3, and to Dr. Trevor Cooke for his help in the care of Case 3.

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VALUE OF HISTAMINE SKIN TESTS IN MÉNIÈRE'S DISEASE

BY

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In 1861 Prosper Ménière (1861a, 1861b) described the disease that bears his name. Little has since been added to his description of apoplectic attacks of vertigo occurring in association with tinnitus and variable but progressive deafness. He suggested that the condition arose in a previously healthy ear, and that the semicircular canals were the site of the functional disturbances. Seventy-seven years later the careful histological studies of Hallpike and Cairns (1938) proved that he had been correct. They demonstrated a gross dilatation of the endolymphatic system, with degenerative changes in the organ of Corti, and an absence of the normal connective tissue around the saccus endolymphaticus. There was no evidence of inflammation or haemorrhage. The pattern of the disease is thus clear and its pathology demonstrated, but the cause of the disturbance in the inner ear is still undetermined. As might be expected, there are many theories, each supported by corresponding methods of treatment. Strangely enough, these treatments are all attended by much the same degree of success (Atkinson, 1945a).

Mygind (1924) and Dederding (1929) suggested a retention of water in the body, of which the disturbance in the labyrinthine and cochlear systems is but a part. Furstenberg *et al.* (1934) believed that there was a retention of sodium chloride rather than of water, while Wright (1937, 1946) maintained that focal infection was the cause of the disease. Crowe (1938) found it difficult to believe that there was some generalized disturbance, because Ménière's disease was so often, at least initially, unilateral, and he concluded that pressure changes in the endolymph were responsible. Eustachian obstruction, labyrinthine haemorrhage, aberrant vessels, and vascular spasm have all had their advocates. Latterly it has been suggested that Ménière's disease is an allergic response and that histamine may be used in its diagnosis and treatment. It is with this theory that this paper is concerned.

Allergy and Histamine Sensitivity

Although a great deal of discussion has been devoted to the conception that Ménière's disease is due to allergy, there is no direct evidence of this. The disease is not familial, it tends to occur in middle life, and other allergic manifestations are not often found associated with it. The indirect evidence may be stated as follows: the pathological process is one of a non-inflammatory extracellular oedema. The symptoms, both cochlear and vestibular, are fluctuant. Often the deafness and tinnitus increase during an attack of vertigo, to improve in the interval. The ultimate course of the disease is variable, too. Some cases have attacks at intervals of months or years, suffering little diminution in hearing; in others the disease is steadily progressive until, finally, complete deafness and an insensitive labyrinth result in a cure of the vertigo. This variability has been put forward in favour of a reversible mechanism that might well be allergic. But only a few actual instances of antigen-antibody type of allergy have been recorded. For this reason Williams (1944, 1947) suggested that some form of physical or intrinsic allergy existed. By this he meant the type first postulated by Duke (1925) in which there is no antigen-antibody reaction, but instead a sensitivity to heat, cold, atmospheric pressure, or to endocrine or emotional factors.

Atkinson (1941, 1943a, 1943b) approached the subject from a different angle. He suggested that Ménière's disease was a "syndrome that can be produced by at least two causes." It was a vasomotor disturbance which in one group of cases was allergic in origin and in the other was due to vasospasm. But he was able to demonstrate hypersensitivity in only two of his cases in the allergic group. He argued that, as it was well known that the final results of allergy in the tissues were due to the liberation of a histamine-like substance, then increased sensitivity to intradermally injected histamine should be a general indication of the presence of allergy. This supposition was based on the work of Dzsinich and Gallé (1939), who had used injections of histamine as an intradermal test in cases of asthma. These authors stated that it was possible to desensitize the tissues to histamine by graded injections of that substance. Shelden and Horton (1940) treated 11 cases of Ménière's disease during the acute attack of vertigo with intravenous histamine and reported dramatic results. This, however, was not surprising, as it is known that the attack of acute vertigo resolves without treatment. Atkinson (1941) adapted the test of Dzsinich and Gallé, using an intradermal injection of 0.01 mg. of histamine dihydrochloride in 0.1 ml. of saline. His patients fell into two groups—histamine sensitive (20%) and histamine insensitive (80%)—as a result of the test. A positive reaction showed a wide area of erythema, 1½ to 2 in. (3.8 to 5 cm.) in diameter, a large weal of ½ to ¾ in. (1.25 to 1.9 cm.) diameter, and long trailing pseudopodia, 1 in. (2.5 cm.) or more long, which appeared in three to five minutes, fading after 20 minutes but still present at the end of 30 minutes. Small buds at the edge of the main weal were not taken as positive. In the normal person—that is to say, the histamine-insensitive group—the erythematous flare was 1¼ to 1½ in. (3.1 to 3.8 cm.) broad, and the weal ¼ to ½ in. (0.8 to 1.25 cm.), both fading somewhat more rapidly than did the positive response. The cases that were found sensitive all responded well to desensitization with histamine. In those patients who did not give a positive skin reaction, Atkinson argued, the symptoms were due to vasospasm. These he treated with nicotinic acid, a vasodilator. Both mechanisms he thought could lead to increased endolymph production in the labyrinth.

Williams (1944) criticized this theory on the ground that he got equally good results in both groups with nicotinic acid, while Rainey (1943, 1945) and Lillie *et al.* (1944), disregarding any form of skin-testing, got good results with histamine only. Farmer (1945) was quite unable to agree that allergic individuals were more sensitive to histamine than normal persons, and concluded that the test was valueless in this respect. But this criticism had already been anticipated by Atkinson (1943b), who withdrew the statement that the test was a true indicator of allergy, but insisted that its results were valid in dividing patients with Ménière's disease into two groups. Atkinson (1945b) then gave more details of his test, and emphasized that it was valid only if one adhered strictly to his method. Further, it was now his

opinion that the size of the flare was of secondary consideration and that *the true criterion of a positive result was the presence of pseudopodia.*

A year later Atkinson (1946a, 1946b) again modified the test. He now uses 0.05 ml. of a 1/10,000 solution of histamine base—that is to say, 0.005 mg. of base in 0.05 ml.—which must be injected into the volar surface of the forearm, 2 in. (5 cm.) below the elbow. The normal response is now stated to be a flare of 1 to 1½ in. (2.5 to 3.8 cm.) diameter and a weal of ¼ to ½ in. (0.6 to 0.8 cm.). In the histamine-sensitive the flare is 2 to 2½ in. (5 to 6.3 cm.) and the weal ¾ to 1 in. (1.9 to 2.5 cm.). Pseudopodia are an essential indicator of sensitivity—sometimes a long trailing one of 1 to 2 in. (2.5 to 5 cm.) length, and sometimes two or more shorter ones. Small buds are not to be considered positive. His work has recently been confirmed in this country by Kodicek *et al.* (1950). The theory and corresponding method of treatment are based on the assumption that in a proportion of patients with Ménière's disease there exists a state of abnormal sensitivity to histamine which can be recognized by an abnormal skin response. Yet no one seems to have published figures of the skin responses of normal persons by this method. I have attempted to do this.

Investigations

Intradermal skin tests were performed on 50 cases of Ménière's disease. There were 35 men and 15 women, and the average age of the whole series was 47 years. In spite of what has been said about the association of the disease with allergy, only two patients suffered from migraine, and one had true asthmatic attacks. None gave a history of urticaria, angioneurotic oedema, hay-fever, or any food sensitivity in relation to the vertigo.

Similar tests were carried out on 50 controls—33 men and 17 women—the average age being 39 years. Twenty-three of these were in normal health, either students or out-patients with no organic disease, and 27 were patients from the medical wards. The only criterion adopted in the selection of either group of controls was that they should not suffer from any allergic disease or migraine.

Methods

Two solutions were used : (A) 0.01 mg. of histamine dihydrochloride in 0.1 ml. of normal saline (equivalent to 1/20,000 histamine base). (B) 0.005 mg. of histamine base in 0.05 ml. of normal saline (equivalent to 1/10,000 histamine base).

These are the first and second solutions advocated by Atkinson. As 1 mg. of histamine dihydrochloride contains 0.57 mg. of histamine base, it can be seen that the absolute quantity of histamine in each solution is almost the same, but B is twice the concentration of A.

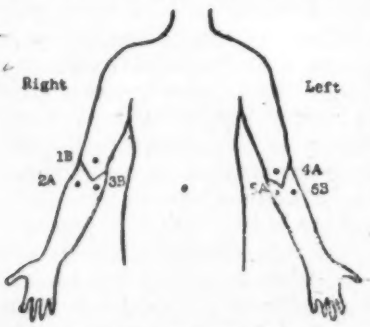

FIG. 1.—Sites used for the injection of solutions of A and B.

Intradermal injections were made on the volar surface of both arms in the region of the elbow. A tuberculin syringe was used, graduated to 0.01 ml. Three sites on each arm were chosen — one just above and two just below the elbow crease. Both solutions A and B were used, being distributed as shown in Fig. 1. The characteristic raised white weal and surrounding red flare developed in every case, and sometimes one or more raised red lines were seen to radiate out from the weal —the so-called pseudopodia (see Fig. 2). After five to ten minutes the appearance had developed to its maximum and the outline was inked on to the skin. A

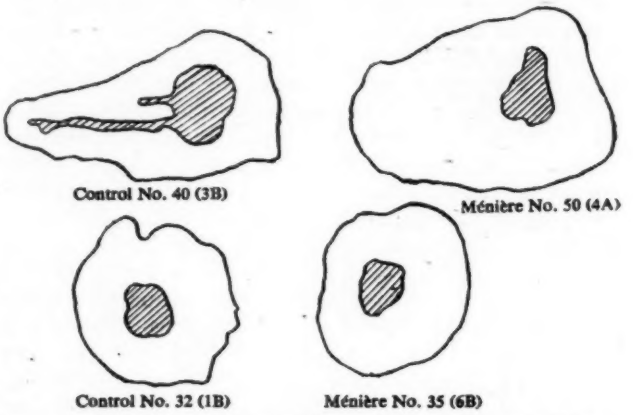

FIG. 2.—Typical examples of skin responses. Half natural size.

piece of "cellophane" paper was then placed over the area and a tracing taken. This was kept as a permanent record and measured. As to the method of measurement, I tried both a planimeter and direct computation from squared graph paper. These are excessively tedious, and are hardly more accurate than the much simpler method of taking the average of two diameters at right angles. I have given the diameters of flare and weal in inches, as this makes comparison with Atkinson's work easier.

Interpretation of Results

The Pseudopodic Processes

1. Atkinson's later and stricter criterion of a positive response is defined as a weal produced by histamine solution B that shows one or more pseudopodia of 1 in. (2.5 cm.) or over in length, at a site 2 in. (5 cm.) below the bend of the elbow (3B and 6B in Fig. 1). Five of the cases of Ménière's disease and eight of the controls were positive.

2. With the above criterion, but including also Atkinson's earlier testing solution A, four sites are available below the elbow (2A, 3B, 5A, and 6B in Fig. 1). Seven of the cases of Ménière's disease and eight of the controls were positive.

3. Again considering as positive a pseudopodium of 1 in. (2.5 cm.) or more in length, with either solution A or B, and including a further site 2 in. (5 cm.) above the bend of the elbow on either side (1B, 2A, 3B, 4A, 5A, and 6B in Fig. 1), 12 cases of Ménière's disease and 13 of the controls were found positive.

4. Lastly, as others (Williams, 1944 ; Farmer, 1945) have taken 1 cm. as the measure of the pseudopodium in judging a positive reaction, I have counted the number of cases, using all six sites and both solutions, that would have to be called positive. By this method 37 of the cases of Ménière's disease and 32 of the controls were positive.

Clearly, whichever dilution of histamine, whichever site, and whichever length of pseudopodium is chosen,

there is no significant difference between the 50 cases of Ménière's disease and the 50 controls. The results are summarized in Table I.

TABLE I.—*The Production of Pseudopodia from a Histamine Weal in 50 Cases of Ménière's Disease and 50 Controls*

Criteria of a Positive Response	No. of Cases	
	Ménière	Controls
1. 1 in. (2·5 cm.) or more long with solution B (sites 3B and 6B)	5	8
2. 1 in. (2·5 cm.) or more long with solutions A and B (sites 2A, 3B, 5A, 6B)	7	8
3. 1 in. (2·5 cm.) or more long with solutions A and B (sites 1B, 2A, 3B, 4A, 5A, 6B)	12	13
4. 1 cm. or more long with solutions A and B (sites 1B, 2A, 3B, 4A, 5A, 6B)	37	32

Finally, it has been observed that the greater the number of tests performed the more likely is it that a pseudopodic process will appear. This is shown in Fig. 3.

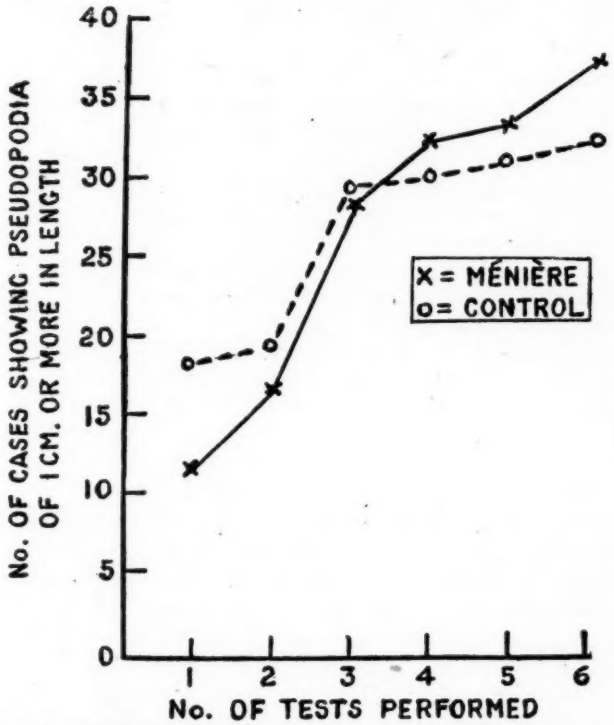

FIG. 3.—Chart showing how the number of cases developing pseudopodia increases with the number of tests performed.

The Weal and Flare

Although Atkinson has now stated that the presence of pseudopodia is more important than the size of the triple response, he still gives measurements of what he believes to be abnormal. The weal in the normal is 0.25 to 0.3 in. (6.4 to 7.6 mm.) and the flare 1 to 1.5 in. (2.5 to 3.8 cm.) diameter. In the histamine-sensitive subject they are 0.75 to 1 in. (1.9 to 2.5 cm.) and 2 to 2.5 in. (5 to 6.3 cm.) respectively. My findings in the 50 cases and 50 controls are shown in Tables II and III. The number of observations does not always add up to 50, because in the first 9 cases and the first 11 controls Atkinson's latest method only was used. In the remainder both solutions and all six sites were employed. The tables are therefore based on the means of 520 different skin tests in 100 persons, but for want of space the individual measurements cannot be given here (see Haggie, 1949). In both cases and controls there was a well-defined variation either side of the mean. The upper and lower limits of weal and flare were 0.4 to 0.9 in. (1 to 2.3 cm.) and 1.4 to 2.9 in. (3.6 to 7.4 cm.) respectively.

TABLE II.—*A Comparison of the Mean Values for Diameter of Weal in Inches, at Six Different Sites in the Cases and Controls*

	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control
Sites:	1B		2A		3B		4A		5A		6B	
Mean	0·57	0·57	0·56	0·53	0·68	0·56	0·6	0·6	0·6	0·61	0·57	0·57
Standard deviation	0·1	0·1	0·08	0·08	0·09	0·08	0·1	0·1	0·1	0·08	0·1	0·1
No. of observations	39	41	39	41	50	50	39	41	39	41	50	50

TABLE III.—*A Comparison of the Mean Values for Diameter of Flare in Inches, at Six Different Sites in the Cases and Controls*

	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control
Sites:	1B		2A		3B		4A		5A		6B	
Mean	2·08	2·16	1·98	1·96	2·09	2·06	2·1	2·1	2·0	2·0	2·0	1·9
Standard deviation	0·23	0·3	0·23	0·26	0·23	0·29	0·27	0·34	0·28	0·27	0·31	0·26
No. of observations	39	41	39	41	50	50	39	41	39	41	50	50

These figures show the mean values and standard deviations to be so nearly identical both in cases and in controls that it can be concluded that there is no difference between them. Further statistical analysis is therefore unnecessary. Even allowing that only 20% of the cases of Ménière's disease show an abnormal response, there should be enough observations here for a difference between the cases and controls to be apparent. In fact there is none.

Summary

Histamine skin tests have been performed by Atkinson's method, and certain modifications of it, on 50 cases of Ménière's disease and 50 controls.

The production of pseudopodic processes from the central weal in Ménière's disease is identical with that in the controls. The greater the number of injections made the more likely is it that a pseudopodic process will appear.

The mean values for the diameter of flare and weal are almost identical at every one of the six sites, and in this respect also there is no significant difference between the cases of Ménière's disease and the controls.

I am indebted to Dr. Russell Brain, who first suggested this investigation; to Mr. Charles Keogh for allowing me to use his cases and his department for the practical work; to Sir Alun Rowlands, Mr. A. Bowen-Davies, and Mr. J. W. S. Lindahl for permission to use their cases; and to Dr. R. R. Bomford for reading the script.

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THE ERYSIPELOID OF ROSENBACH

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Erysipeloid infections of the hand are generally considered to be uncommon. This impression is supported by the scant references to the condition in many of the popular textbooks and by many of the recent papers dealing with the clinical aspects of the infection. However, it has also been suggested that this apparent rarity is due to frequent misdiagnosis (McNeill Love, 1949). Casualty officers working near meat and fish markets, slaughterhouses, and hotel districts are quite familiar with the disease and regard it as being by no means uncommon. In most of the reported cases the diagnosis has depended solely on clinical grounds, and it has been argued that, as the clinical picture is so typical, biopsy with subsequent isolation of the causative organism is neither necessary nor justifiable (Goodwin, 1950).

Biopsies were performed in a number of the cases reported in this communication, and the results of this bacteriological investigation will be detailed later.

Clinical Features

The clinical picture is a very typical one and was uniform in all our cases. The original description was published by Morrant Baker (1873), who named the condition "erythema serpens." We agree with the observations of Rosenbach (1887), who stated: "The symptomatology is characteristic, and anyone having once seen the condition can readily make the diagnosis."

The patient complains of pain and swelling of a finger or part of a hand. The pain is often severe, is made worse by the application of heat, and is described as throbbing or burning. A history may be elicited of a scratch or puncture of the affected part by a meat bone, fish bone, fish skin, or butcher's knife, perhaps as long as two weeks before the onset of symptoms, but often no definite history of trauma is obtainable. Symptoms may have been present for several days or even weeks before the patient attends for treatment. It has been noticed that patients in the present series attended earlier if one of their workmates had previously been infected and had received treatment. The employees of a firm of Continental butchers were prominent for their early attendance.

Examination reveals a moderately inflamed swollen finger or part of the hand. Some evidence of the original injury is often visible as a stretched greyish scar. The swelling involves both the skin and the subcutaneous tissue, the margin of the skin-swelling is well defined, and the area of affected skin is dusky in colour. Although the patient complains of severe pain, tenderness is nothing like so apparent as in pyogenic infections of a similar area. Quite firm palpation of the infected part is tolerated. Associated lymphangitis and lymphadenitis are uncommon, and it is probable that their presence is indicative of secondary infection. Systemic effects have been described, but are uncommon.

Erysipeloid is a self-limiting condition. It is subject to spontaneous remission and ultimate resolution without suppuration, physical signs being present usually for a period of three to four weeks. Incision of the infected area benefits neither symptoms nor progress, and may result in secondary infection.

Clinical Cases

Two series of cases collected at King's College Hospital during 1948 and 1949 are reported. All presented the clinical features already described. The patients in the 1949 series were subjected to biopsy, and attempts were made to recover the causative organism. In three instances (Cases 2, 6, and 11) penicillin had unfortunately been administered before the biopsy was performed.

It will be noticed (Fig. 2) that no case was recorded during the first five months of 1949. This may have been due to failure to recognize the condition during this period. A search through the records, however, failed to reveal any hand infections with suggestive physical signs presenting at this time.

1948 Series

Thirty-one cases were seen which conformed to the clinical picture described. The seasonal incidence is shown in Fig. 1. The occupations of the patients were: housewives, 8; fishmongers, 8; butchers and poulterers, 6; bacon cutter, 1; unrecorded, 8. A definite history of trauma from a possible source of infection was obtained in 12 instances. Eleven other patients admitted to the frequent occurrence of such trauma but were unable to implicate a specific instance. The possible sources included beef, mutton, and pork bones, poultry and rabbit bones, fish bones, and meat knives. Skate was the fish most often blamed. The duration of symptoms before attending hospital varied from one day to six weeks.

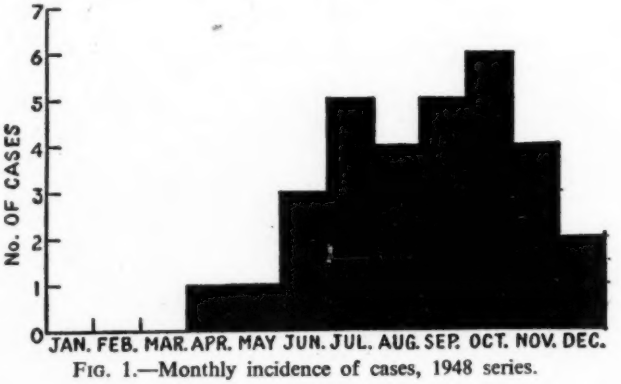

FIG. 1.—Monthly incidence of cases, 1948 series.

All the patients were treated with systemic penicillin. All but three received penicillin in aqueous solution, 250,000 units twice a day. The other three received penicillin in oil, 300,000 units daily.

Owing to misdiagnosis two patients initially received sulphadiazine, but penicillin was administered after the diagnosis had been made. Two patients who relapsed received sulphadiazine as well as penicillin after the relapse.

In most cases treatment lasted from one to four days. After this time the patients usually defaulted, presumably because their symptoms had subsided.

Only three patients other than the six who relapsed required treatment for more than four days. One patient persisted in attending for five days because of slight aching of the finger, the erythema having subsided after two days' treatment. A second case was undiagnosed for six days, and resolved spontaneously after a further two days. The third patient had noticed symptoms for six weeks and, for no good reason, received sulphadimidine for six days, after which resolution occurred.

Six relapses are known to have taken place. As in the rest of the series, initial treatment had lasted from one to four days. Relapses occurred three to eight days after penicillin administration had ceased. Further penicillin was given for two or three days, when, except in one instance, the patients ceased to attend. The exception received treatment for 13 days after relapse, and penicillin therapy, continued for seven days, failed to effect resolution. Oral sulphadiazine was administered, with doubtful effect, for a further six days, by which time symptoms had subsided.

1949 Series

Twenty cases were seen, in all of which a biopsy was taken immediately the clinical diagnosis was made (Table I). Unfortunately, in three cases penicillin had been started before the correct diagnosis was made, and this may have vitiated the results in these instances.

TABLE I.—*1949 Series*

No.	Date	Sex	Occupation	Probable Infecting Agent	Result of Culture	Progress
1	26/6/49	F	Housewife	Meat knife	+	Relapsing
2	30/6/49	M	Continental butcher	" "	−	"
3	3/8/49	F	Housewife	Fish bone	+	Uneventful
4	23/8/49	M	Fruiterer	—	−	"
5	5/9/49	M	Continental butcher	Meat knife	−	"
6	10/9/49	M	"	"	−	"
7	16/9/49	M	Cook	Chicken bone	+	"
8	22/9/49	F	Housewife	Cat scratch	+	"
9	26/9/49	F	Dressmaker	? Human placenta	+	"
10	26/9/49	F	Housewife	—	−	Relapsing
11	30/9/49	M	Fishmonger	Fish bone	−	"
12	11/10/49	M	Butcher	Rabbit bone	−	Uneventful
13	12/10/49	M	Continental butcher	Meat knife	+	"
14	14/10/49	M	—	—	−	"
15	19/10/49	M	Furrier	—	−	"
16	28/10/49	F	Housewife	Fish bone	−	"
17	2/11/49	M	Fishmonger	" "	−	"
18	20/11/49	F	Housewife	—	−	Relapsing
19	27/11/49	M	—	—	+	Uneventful
20	6/12/49	F	Housewife	Meat knife	−	"

So far as possible biopsy was performed before treatment was started. The skin was cleaned with cetrimide ("cetavlon") and carefully dried. With 1% procaine an intradermal weal was raised in the demarcated edge of the lesion. A small whole-thickness fragment of skin was excised from the edge of the lesion by the "pinch" method. The specimen obtained was immediately placed in glucose broth and transferred to the laboratory for culture.

Free oozing of blood from the wound was easily controlled by firm pressure with a sterile dressing. No complication occurred as a direct result of the biopsy, and in every case healing was normal as in healthy skin.

This series of cases, taken in conjunction with the 1948 series, gives some indication of the frequency with which the disease is seen in the various seasons. The seasonal incidence for the 1949 series is shown in Fig. 2. The duration of symptoms prior to attendance for treatment was of a similar order to that of the 1948 series.

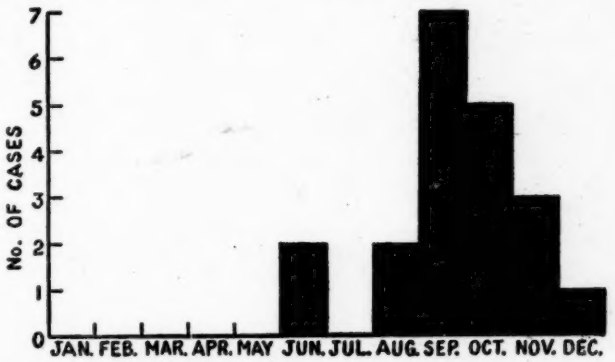

FIG. 2.—Monthly incidence of cases, 1949 series.

Every patient received penicillin either as twice-daily injections of 250,000 units of the aqueous solution or as a single daily injection of 600,000 units of procaine penicillin with aluminium monostearate.

Fifteen of the 20 patients in the series received penicillin for periods varying from one to twelve days. The shorter periods were due to default by the patients concerned. The other five cases relapsed whilst under treatment or after cessation of treatment, and penicillin administration was continued or started again in these. In each of these relapsing cases an average period of one month elapsed before resolution occurred.

Follow-up inquiries were sent to all patients. No reply was received from five, none of these being in the relapsing group. Of the other 15, five had relapsed and returned for treatment, while 10 reported that no relapse had occurred subsequent to treatment.

An analysis of the results of treatment with penicillin is detailed in Table II.

TABLE II.—*Follow-up of 1949 Series*

Patients returning Questionary:	
No. symptom-free within 3 days	4
" " " in 3–6 days	3
" " " 6–12 days	4
" with symptoms after 12 days	4
Total	15
Patients failing to return Questionary:	
No. defaulting within 6 days	5

Thus of the 15 patients of whom we have full details, 7 (47%) were symptom-free within six days, and 11 (73%) within 12 days. In an infection such as erysipeloid, in which symptoms may be rapidly relieved by penicillin, there is a tendency for those rapidly cured to default, and for those who relapse to return for further treatment. It is not unreasonable to assume that some, at least, of the five patients who defaulted and did not reply to the follow-up questionary remained symptom-free. If this is the case, the cure rates quoted above are unduly pessimistic.

The duration of treatment compares unfavourably with that quoted in previous papers on the subject (King, 1946), but the criteria of cure probably vary from clinic to clinic, and after our experience with some relapsing cases we were reluctant to withdraw penicillin too soon. Treatment was continued until all symptoms and signs had disappeared.

Erysipelothrix rhusiopathiae was cultivated in only seven of the twenty cases. Of these seven cases one relapsed after treatment. Three cases of the thirteen which failed to yield the erysipelothrix received some penicillin before biopsy was performed. Two of these three cases were members of the relapsing group. Excluding the relapsing group, the clinical courses of the six erysipelothrix-positive cases and the nine erysipelothrix-negative cases were similar. The strains isolated from these patients are the subject of a separate communication (Sneath, Abbott, and Cunliffe, 1951).

It is interesting that Case 1 failed to respond rapidly to penicillin although the erysipelothrix recovered from her biopsy specimen was sensitive to penicillin *in vitro*.

Discussion

Although several clinical types of erysipeloid have been described we have considered only the localized variety, as this was the sole type to come under our care.

On clinical diagnosis alone the numbers involved in our two series suggest that the disease is by no means uncommon. Case 12 of the 1949 series was referred from an out-patient department with the diagnosis of "low-grade infection of the finger." To us the clinical picture was characteristic and the clinical course was typical. It seems likely that many similar cases must occur in which the diagnosis is missed.

The monthly incidence in the two series appears to corroborate the seasonal incidence previously reported (King, 1946; McNeill Love, 1949; Boroda, 1949; McIntyre, 1950).

Even though the condition does not always respond rapidly to treatment an early correct diagnosis is an advantage. One patient in the 1948 series had erysipeloid for six weeks before attending for treatment. By then she had become much disturbed by the duration of the disease. A confident diagnosis and prognosis did much to allay her fears, and subsequent progress was satisfactory, although it is doubtful whether treatment played any significant part in her recovery.

The sources of the infection were diverse. A definite association with meat or fish is common in our experience, skate being the fish most often implicated. Its skin as well as its bones can apparently cause infection.

In the 1949 series unusual causative factors were suggested in two patients whose skin biopsies both yielded positive cultures. Case 8 followed a cat scratch, and Case 9 acquired the infection through burning a finger whilst incinerating a human placenta. The association with a burn has been observed before, although the diagnosis was not proved bacteriologically (Boroda, 1949).

From the two series no definite conclusions can be drawn about treatment. Penicillin often causes rapid amelioration of symptoms, and rapid cure is frequently achieved (47% in six days in the 1949 series). It has been impossible to decide the optimum duration of treatment, as patients often fail to continue their attendances when their symptoms diminish. It is our clinical impression that the likelihood of recurrence is reduced if therapy is continued until all symptoms and signs, such as discoloration and stiffness, have disappeared. Relapses have been very frequent in those cases in which penicillin was withdrawn when some brownish discoloration of the skin was still apparent.

The value of biopsy in these cases must be discussed. It is always more satisfying to confirm a moderately certain clinical diagnosis, if the necessary ancillary investigation does not carry undue risk and inconvenience to the patient. In our experience biopsy of the edge of the lesion has given rise to no unfortunate sequelae in 20 patients. However, our proportion of positive cultures has not been high enough to prove that the procedure is diagnostically of great value. Blame for part of this may be laid on errors in biopsy technique. The erysipelothrix is a delicate organism whose growth seems to be easily inhibited by cetrimide, the cleansing agent used in all our cases (Sneath, Abbott, and Cunliffe, 1951).

Against this may be balanced the fact that it has been possible to isolate several strains of the erysipelothrix and to study its bacteriology and sensitivity to various antibiotics. In this way progress can be made in the study of the disease and its treatment.

Summary

Two series of cases of erysipeloid of the hand are reported, skin biopsies of the second series being cultured.

The condition is not uncommon, but probably the diagnosis is often missed.

In the 1949 series 47% of the patients were symptom-free in six days and 73% in 12 days after treatment with parenteral penicillin.

We would like to thank Sir Cecil Wakeley, senior surgeon, King's College Hospital, for advice and encouragement, Mr. E. G. Muir, surgeon to the Casualty Department, King's College Hospital, for permission to publish our work on these series of cases, and Dr. D. I. Williams for his helpful criticism in the preparation of this paper.

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The Institute of Almoners has opened a supplementary register for certain of those almoners at present employed in the National Health Service who do not hold the Institute's own certificate of qualification. The supplementary register will be open until December 31, 1951, and admission will be according to experience and qualifications. Those applying must be over 30 years of age, engaged in medico-social work in a hospital, and known as almoner both at the time of application and continuously for three years prior to July 5, 1948. All persons admitted to the supplementary register will be entitled to apply for a special category of membership of the Institute. This will bring them generally under the aegis of the Institute in all professional matters, including negotiations for salaries and conditions of service.

THE BACTERIOLOGY OF ERYSIPELOID

BY

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The published descriptions of *Erysipelothrix rhusiopathiae* vary a good deal, and there is no recent full comparison of human strains with those from animals. We therefore examined in detail, including serology and sensitivity to antibiotics, the seven strains isolated from the patients with erysipeloid whose case histories are described by Price and Bennett (1951) at page 1060 of this issue and compared them with strains from other sources.

Sources of Material.—Human strains: Seven strains isolated by us (K13, K19, K45, K49, K53, K79, and K176) and two by Dr. Mary Barber (9 and 21). *Animal strains:* Seven received from Dr. A. W. Gledhill (D, R, V, EW2, EW16, EW24, and MEW22) and two from Dr. D. Riding (PV174 and SE46).

Method of Isolation

Biopsy specimens from the skin of 20 patients were cultured. The specimens were taken from the spreading edge of the erysipeloid and included the entire thickness of the dermis; they were placed whole in 1% glucose broth and incubated aerobically at 37° C. for one week. The broth was subcultured aerobically and anaerobically every other day on blood-agar plates. All broths yielding *E. rhusiopathiae* became turbid within 48 hours. The strains isolated from the seven positive skin samples were preserved by freeze-drying within a few days of isolation.

We examined these strains in detail together with Barber's two human strains (9 and 21) and two veterinary strains (D, isolated from a duck, and PV174, from swine erysipelas). There were no appreciable differences as regards microscopical or colonial morphology or biochemical activity among any of these strains, except that PV174 grew rather more slowly than the others.

Description of our Strains

Morphology on Horse-blood Agar.—Small slender rods about 0.4 μ by 2.5 μ in size, straight or slightly curved, single, and forming unbranched chains or filaments up to about 20 μ long. In old cultures longer forms predominated. Gram-positive, evenly staining but easily decolorized; not acid-fast, non-motile, forming no spores. No capsules detected. All the strains were smooth colonially, but the microscopical appearance, even on primary isolation, was closer to the "intermediate" type described by Barber (1939), consisting mainly of chains of medium length and few single bacilli.

Cultural Appearances

Horse-blood-agar Plate.—Aerobically; 37° C. *Twenty-four hours:* Small round, glistening, transparent colonies about 0.2 mm. in diameter. *Forty-eight hours:* Colonies 0.6 mm. in diameter, round, low convex; surface smooth and shiny, with entire or slightly undulate edge and surrounded by a narrow zone of alpha-haemolysis; butyrous and easily emulsified. Agar pitted on removal of colony. *Seven days:* Colonies 2 mm. in diameter, flattened, with a low central papilla, radial striations, and a lobate edge. Haemolysis and dark central pigment well marked. Colonies grown anaerobically very similar in shape and size.

Nutrient-agar Plate.—Colonies similar to those on blood agar, but a little smaller. Central patches of brown pigmentation visible at 48 hours and more pronounced after further incubation.

Gelatin Stab at 22° C.—Twenty-four hours: Faint hazy growth a few millimetres below the surface. *After a few days* the constant and characteristic feature was the column of uniform diameter running from top to bottom of the medium, composed of fine horizontal outgrowths from the stab line (the classical "lampbrush"). No liquefaction within 14 days. The swine strain PV174 differed from all other tested strains by growing poorly in the depth.

Broth.—Slight turbidity with powdery deposit after 24 hours, easily broken up. Deposit stringy after a few days. No pellicle. Odour characteristic and suggestive of stewed beef. The addition of 2% serum or 0.2% glucose to broth gave rather better growth.

1% Glucose-agar Shake.—37° C. *Twenty-four hours:* Uniform growth of minute discrete colonies throughout the medium.

Other Tests

Biochemical.—The reactions of all 11 strains were identical when tested with 1% sugar in 1% peptone. Acid, without gas, was formed in glucose, lactose, fructose, galactose, and mannose; in xylose a very small amount of acid was produced. No acid production was detected after 14 days' incubation in maltose, sucrose, mannitol, dulcitol, salicin, arabinose, rhamnose, adonitol, inositol, erythritol, dextrin, starch, glycogen, inulin, amygdalin, aesculin, raffinose, cellobiose, melibiose, melezitose, trehalose, sorbose, and sorbitol. A trace of acid but no clot in litmus milk, Methyl red, Voges–Proskauer, and tests for indole and ammonia, for nitrate and methylene-blue reduction, for hydrolysis of sodium hippurate, and for urease and catalase were negative. A moderate degree of phosphatase activity was detected (Bray and King, 1943). No growth in Koser's citrate. All strains produced H_2S.

Metabolism.—Growth was approximately equal under aerobic and anaerobic conditions, and was not appreciably affected by the addition of 10% CO_2 in either atmosphere. The optimum temperature for surface growth on blood agar is 30° C. to 40° C. Growth occurred in broth from *pH* 6.7 to 9.2, with an optimum at *p*H 8 to 8.5. In peptone water, growth was invariably scanty. No soluble haemolysin for horse, sheep, human, rabbit, or guinea-pig red cells.

Pathogenicity.—All our strains killed mice within four days of a subcutaneous inoculum of 0.01 ml. of a 24-hour broth culture. The mice developed a typical conjunctivitis, and post-mortem cultures from heart blood and spleen were positive in every case.

Resistance.—Broth cultures were killed at 60° C. within five minutes. When *E. rhusiopathiae* was heavily inoculated into broth containing 10% sodium chloride the cultures became sterile within 24 hours at 37° C.

Sensitivity to Dyes and Antibiotics

In view of the possible uses of selective media, nutrient agar containing tenfold dilutions of various bacteriostatic substances, from 1:1,000 to 1:1,000,000, was lightly inoculated and incubated at 37° C. for 24 hours. The behaviour of each of the 11 strains tested was identical; the results are shown in Table I.

All strains grew scantily on MacConkey's agar in 48 hours, and not at all on potato or Hoyle's tellurite agar.

TABLE I.—*Effect of Various Bacteriostatic Substances on Growth of E. rhusiopathiae*

	Concentration Completely Inhibiting Growth	Concentration Permitting Free Growth
Sodium azide	>1:1,000	1:10,000
Potassium tellurite	1:100,000	<1:1,000,000
Sodium biselenite	1:1,000	<1:1,000,000
Methylene blue	1:10,000	<1:1,000,000
Thionine	1:1,000	1:1,000,000
Basic fuchsin	1:1,000	1:100,000
Pyronine	>1:1,000	1:10,000
Crystal violet	1:10,000	1:1,000,000
Brilliant green	1:100,000	<1:1,000,000
Acriflavine	1:100,000	1:1,000,000
Cetyl ammonium bromide (cetrimide)	1:100,000	1:1,000,000

The sensitivity to various antibiotics (Table II) was tested as follows: varying amounts of antibiotic were added to nutrient agar (*p*H 7.4–7.6) at 50° C.; plates were poured, dried, and inoculated over an area the size of a sixpence with a loopful of a 1:10 dilution of an overnight broth culture of the organism to be tested.

TABLE II.—*In vitro Sensitivity of E. rhusiopathiae*

Chemotherapeutic Agent	Range of Inhibitory Concentration for *E. rhusiopathiae*
Sulphathiazole	>5 mg./100 ml.
Penicillin	0·06–0·12 unit/ml.
Streptomycin	12·5–50 µg./ml.
Aureomycin	1·5–2·5 µg./ml.
Chloramphenicol	5–9 µg./ml.
Polymyxin E	>80 µg./ml.

Strains tested: K13, K19, K45, K49, K53, K79, K176, 9, 21, PV174, R, D, MEW22, EW2, EW24, EW16.

Results were read after 24 hours' aerobic incubation at 37° C. The *in vitro* sensitivity to penicillin, chloramphenicol, and "aureomycin" was such that all strains fell within the therapeutic range of these drugs; all, however, were resistant to the usual therapeutic blood-concentrations of sulphathiazole and polymyxin E. There were considerable individual variations in the degree of resistance to streptomycin; some strains, however, were susceptible to concentrations equal to those obtainable in the blood.

These findings are in accordance with therapeutic experience: thus many workers—for example, Klauder and Rule (1944), Barber, Nellen, and Zoob (1946), and King (1946)—found sulphonamides useless in the treatment of human erysipeloid, and Klauder and Rule (1946) concluded that streptomycin had little effect in experimental mouse infections. On the other hand, successful therapeutic responses to penicillin are now well known in both human and experimental disease, and the observations of our colleagues (Price and Bennett, 1951) bring further evidence on this point. In view of the *in vitro* tests both aureomycin and chloramphenicol would seem worthy of clinical trial, though in the treatment of experimental infections in birds Prier and Alberts (1950) reported penicillin to be more effective than aureomycin.

Antigenic Structure

From the work of Watts (1940) and Gledhill (1945) it appears that the species has several thermostable O antigens, which are distributed in varying amount among the individual members of the species, and that every strain is agglutinated by antiserum prepared against any other strain. All our strains were agglutinated to titre by a polyvalent swine erysipelas antiserum. By cross-absorption Gledhill (1945) has distinguished several antigenic groups in his strains of animal origin. We immunized rabbits with boiled organisms of his Groups I, II, III, and IV, and prepared group-specific sera by absorption with heterologous strains. Unfortunately the titres fell very considerably as a result of absorption.

Table III shows the results of testing these sera against our strains by Gledhill's methods. As saline suspensions tend to be unstable and frequently show fine degrees of agglutination, almost complete agglutination was taken as the end-point. Two of our strains appeared to fall into Gledhill's Group I, one into Group III, one into Group I+II, and one into Group I+III; two we were unable to type. Gledhill found that about one-third of his strains were of Group I, one-sixth of Group II, one-sixth of Group III, the remainder being of other types, such as IV and I+II, or untypable. Thus the human strains are distributed amongst the same groups as animal strains.

TABLE III.—*Agglutination of Individual Strains of E. rhusiopathiae by Group-specific Sera*

Strains	Titres to Antisera				Presumed Group
	Group I	Group II	Group III	Group IV	
	Anti-D Absorbed a EW2 (II) and EW16 (III)	Anti-EW2 a Absorbed a D(I) and EW16 (III)	Anti-EW16 Absorbed D(I) and EW2 (II)	Anti-MEW22 Absorbed a D(I) and EW16 (III)	
Type strains:					
Group I D	160	20	—	—	
Group I R	40	—	—	—	
„ II EW2	—	40	—	—	
„ II EW24	—	80	—	—	
„ III EW16	—	—	80	—	
„ III V	—	—	40	—	
„ IV MEW22	—	—	—	40	
Unknown strains:					
K13	80	—	—	—	I
K19	80	—	—	—	I
K45	—	—	20	—	III
K49	—	—	—	—	Untypable
Human K53	80	80	—	—	I+II
Human K79	160	—	80	—	I+III
Human K176	—	—	—	—	Untypable
Human 9	—	—	40	—	III
Human 21	20	20	—	—	Doubtful
Porcine PV174	40	—	—	—	I
Porcine SE46	—	—	80	—	III

Titre expressed as reciprocal of serum dilution. — = less than 20.

Discussion

Though easily cultivated when once isolated, there is general agreement that *E. rhusiopathiae* is not easily grown from human erysipeloid by the usual methods of sampling; for successful isolation it would seem necessary to perform a biopsy which includes the whole thickness of the skin (Düttmann, 1921; Barber, Nellen, and Zoob, 1946). In our series 7 out of 20 biopsy specimens were positive for *E. rhusiopathiae*; several cultures remained sterile; in the majority of positive isolations growth was obvious within 24 hours (Table IV).

The explanation of our failure to isolate erysipelothrix from a higher percentage of specimens is not clear, but may be due to: (1) Patchy or scanty distribution of erysipelothrix in the tissues. In a recent isolation the organism was grown only from a second biopsy. In this case it is suspected that the first biopsy had not been taken from the active spreading edge of the lesion.

TABLE IV.—*Results of Culture from Skin of 20 Patients Diagnosed Clinically as Erysipeloid*

Case No.	*E. rhusiopathiae*	Other Organisms
1	+	—
2	−	Aerobic spore-bearing bacillus
3	+	—
4	−	—
5	−	*Cl. welchii*
6	−	—
7	+	—
8	+	Coagulase-negative staphylococcus
9	+	—
10	−	Coagulase-negative staphylococcus
11	−	" " "
12	−	—
13	+	Coagulase-negative staphylococcus
14	−	—
15	−	—
16	−	Coagulase-negative staphylococcus
17	−	Coliform bacillus
18	−	—
19	+	—
20	−	—

It may be noted also that the length of clinical history before biopsy varied from a few days to several weeks, and that three patients had received penicillin before biopsy. (2) Unsuitability of the medium for certain fastidious strains. (3) Inability of the organism to grow out from the centre of a dense piece of tissue. (4) Inhibitory effect of cetrimide used in cleaning the skin, or of local analgesic solutions. (5) The lesions sampled were manifestations of diseases of different aetiology but similar clinical features.

From the data of our colleagues Price and Bennett (1951) there are grounds for considering that this last explanation is unlikely. The other organisms isolated from our biopsy material certainly are not likely to have any aetiological importance; coagulase-negative staphylococci, the commonest of skin saprophytes, were recovered in five instances, and *Clostridium welchii*, aerobic spore-bearing bacilli, and coliform bacilli were each found on one occasion; *Cl. welchii* is well recognized as one of the most ubiquitous of anaerobic bacteria.

The presence of these organisms in our cultures, however, may have adversely affected our results, since in a fluid medium contaminants are apt to overgrow erysipelothrix. The use of a selective medium might increase the proportion of isolations. For this reason we tested the effect of various bacteriostatic substances (Table I). In its sensitivity to dyes *E. rhusiopathiae* resembles most Gram-positive organisms, but is similar to the haemolytic streptococcus in its comparative resistance to crystal violet. Our strains grew well on blood agar at *p*H 6.8 containing 1:1,000 sodium azide and 1:100,000 crystal violet (Packer, 1943).

In view of the long survival of this organism in salted meat (Edwards, 1931) it is perhaps surprising that it dies so rapidly in broth containing 10% sodium chloride. The salt concentration, however, is seldom uniform throughout a piece of pickled meat, and varies very greatly according to the method of salting.

There is much confusion in the literature about the fermentation reactions of erysipelothrix. We believe that much of it is due to the small amount of acid produced, even in glucose; results may vary with the indicator and composition of the medium. We obtained doubtful reactions with one batch of maltose, arabinose, and cellobiose, in which all the strains produced a trace of acidity: on repetition with fresh batches the reactions were all negative. Observations by Woodbine (1950) also suggest that many discrepancies in fermentation reactions may be due to differences in the medium employed; he finds that, whereas maltose is invariably fermented in the presence of 5% bovine serum, no fermentation of this sugar occurs in unenriched peptone water, and that if horse serum is used maltose fermentation is variable. We have not had an opportunity of confirming this statement, as we used unenriched peptone water for all our tests. We cannot, however, confirm Woodbine's failure to obtain growth in litmus milk. Hutner (1942) has shown that the growth of erysipelothrix in simple media is greatly improved by traces of oleic acid and riboflavin; it is possible that variations in the amounts of these substances in different peptones may account for the conflicting reports concerning the ability of erysipelothrix to grow in peptone water. The results obtained in testing for hydrogen sulphide may likewise vary with the medium or method used. All our strains produced hydrogen sulphide in some quantity, as shown when screw-capped agar slope cultures were tested by lead-acetate paper. In general our findings are in good agreement with the more extensive studies of Deem and Williams (1936), Karlson (1938), Barber (1939), and Julianelle (1941).

In the erysipelothrix group three species were differentiated by Rosenbach (1909)—*murisepticus*, *porci*, and *erysipeloides*, those isolated from mouse septicaemia, swine erysipelas, and human erysipeloid respectively. Our failure to find any morphological, cultural, or biochemical differences between human strains and those isolated from animals merely adds further weight to the opinion first advanced by Rickmann (1909) and supported by many later workers that there is insufficient evidence to warrant this classification, and we follow the practice of Topley and Wilson's *Principles of Bacteriology and Immunity* (1946) in contradistinction to that of Bergey's *Manual* (1948) in regarding the three organisms as belonging to one species, *E. rhusiopathiae*.

There is evidence, however, that there are considerable strain differences in virulence; thus, whereas pigs are susceptible to inoculation with the organisms isolated from acute swine erysipelas, attempts to infect them with erysipelothrix isolated from an epizootic in lambs (Cornell and Glover, 1925) were unsuccessful; lambs which are resistant to infection with virulent porcine organisms were readily infected with this strain. Similarly, field mice, which are also said to be normally insusceptible to erysipelothrix infections, have been the subject of a widespread epizootic in California (Wayson, 1927). We have not made a careful study of the pathogenicity of the organisms we isolated; all, however, were highly virulent to laboratory mice.

The Relation of Human to Animal Infections

As to the virulence of animal strains for man, little direct evidence exists. Rosenbach (1887) and Ohlemann (1904) developed erysipeloid after inoculating their forearms with cultures of erysipelothrix, but both cultures were ones which had previously been isolated from human lesions. However, Rahm (1919), in discussing the aetiology of human erysipeloid, refers to numerous infections among veterinary surgeons following needle pricks from syringes containing living cultures and among laboratory workers from broken culture tubes. These cultures would almost certainly have been porcine in origin.

Erysipeloid has for many years been recognized in Europe and America as an occupational disease of

abattoir employees, butchers, kitchen workers, and those handling fish; Klauder (1938), in reviewing 100 cases, was able to obtain a history of contact with animals, fish, or animal products, such as hides, in nearly every case. Epidemiological evidence therefore strongly suggests that man becomes infected through contact with animals or animal material, though in most cases, it must be admitted, the infection of this material has been inferred rather than proved. The relative infrequency of erysipeloid in those tending sick pigs (Bierbaum and Gottron, 1929) is surprising, for it would be thought that farm workers and veterinarians would be as liable to trauma as, say, butchers or workers in a button factory. The prolonged survival of virulent organisms in inanimate material; the natural history of outbreaks of swine erysipelas, pointing to soil infection rather than to spread from other centres of infection (Edwards, 1931); and the independent infections of other animals—for example, sheep and field mice—with organisms having a specially high virulence for that species, have led many to suggest that erysipelothrix may lead a saprophytic existence outside the body.

McGinnes and Spindle (1934), in investigating the erysipeloid epidemic among workers in a bone-button factory, noted that the incidence was highest among those who were not only liable to traumatic injury but also working under moist conditions; and in the well-known Odessa epidemic, in which about 200 cases of erysipeloid occurred within two months of the landing of large quantities of a fish of the perch-pike species, Stefansky and Grunfeld (1930) noted that the lesions were typically preceded by a wound from the teeth or fins of the fish during cleaning; again conditions would be moist and, as such, favourable to the spread of saprophytic organisms. The fish appeared healthy but were not examined bacteriologically. Schoop (1936), in Germany, and various workers in Japan, however, have since reported erysipelothrix infections in mice inoculated with slime from the surface of healthy fish of various species.

Evidence, however, is accumulating that *E. rhusiopathiae* may be more widely distributed in the animal kingdom than was formerly thought. It is said to occur fairly commonly in birds of most species (Gledhill, 1948), and, in reviewing the literature, Woodbine (1950) refers to reports of isolated infections in the kangaroo, dog, horse, wild boar, reindeer, and mink; he considers, however, that natural infection in fish has yet to be proved. Of considerable importance, perhaps, are the very occasional reports of infection in rats (Crougue, 1936; Stiles, 1944; Drake and Hall, 1947), because if, as Drake and Hall suggest, erysipelothrix infections in the brown rat are more common than supposed, many puzzles in the epidemiology of erysipelothrix infections may be solved.

Our antigenic studies are by no means complete, but we could recognize certain major antigenic components in our organisms and assign many of them to Gledhill's groups. Though the numbers are small, it is, we think, significant that the strains recovered within the space of a few months from patients with human erysipeloid in a small area of London are distributed amongst the same groups as Gledhill's veterinary strains. Thus our studies emphasize once again how closely related are human strains to those found in animals, and they provide no reason for assuming that human strains are peculiarly virulent for man.

Summary

Erysipelothrix rhusiopathiae was isolated from seven out of twenty patients with erysipeloid.

The seven strains were culturally and biochemically homogeneous and indistinguishable from veterinary strains.

They were distributed among several antigenic groups, and were relatively uniform in their sensitivity to each of various antibiotics. They were most sensitive to penicillin, aureomycin, and chloramphenicol.

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The new factory of Ethicon Suture Laboratories, Ltd., opened at Fountainbridge, in Edinburgh, on October 19, cost about £30,000 to build and equip, and employs 58 men and 131 women. By 1939 approximately half the sutures used in Britain were made in the country, either at Edinburgh or in other factories, and the other half were imported from America. During the war great progress was made by the industry, and at the end of the war Britain was almost self-sufficient so far as sterilizing was concerned, but 50% of the raw strings had to be imported. It is estimated that Britain will now be able to produce all the catgut strings used in our hospitals. The raw material used in the manufacture of sutures is the upper part of the intestine of sheep. The first operation at the factory is that of washing and opening out the hanks, which are then split into ribbons and processed to remove all mucus. The gut is next spun into strings, which are dried, polished, and gauged. The laboratory controls all these processes, and after sterilization further tests are made before the suture is finally packed ready for use. The new factory will house the full "raw" process, and only the final work will be done at the Sighthill factory.

INTRATHECAL CHLORAMPHENICOL IN STAPHYLOCOCCAL MENINGITIS RESISTANT TO PENICILLIN AND STREPTOMYCIN

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Chloramphenicol, an antibiotic first isolated from *Streptomyces venezuelae* (Ehrlich *et al.*, 1948), has recently been prepared synthetically (Olive, 1949). It is a crystalline chemical substance with a wide therapeutic range. It is soluble in water to a concentration of 2.5 mg. per ml. at 25° C., and solutions withstand boiling for five hours without measurable loss of potency. The antibiotic shows considerably more activity against Gram-negative organisms than against Gram-positive and acid-fast species. It is seven to thirty times as active as penicillin against tested Gram-negative species, but much less active against *Staphylococcus aureus*. The range of inhibiting concentration for the organism appears to lie between 1 and 16 μg. per ml. The drug may be administered orally or rectally. A review of the literature reveals no record of the use of intrathecal chloramphenicol in the treatment of pyogenic meningitis. We believe this to be the first record of the administration of chloramphenicol by this route.

Case 1

A man aged 44 was operated on for the exploration of a cerebellar tumour on February 14, 1951. A midline cerebellar haemangioblastoma was completely and successfully removed, and routine penicillin was administered in doses of 250,000 units six-hourly. On the third post-operative day the patient complained of increasingly severe occipital headache, worse on the left side. His temperature rose to 103° F. (39.4° C.), and 48 hours later he developed a free discharge of blood-stained pus from the right side of his scalp incision. A direct film stained by Gram's method showed numerous pus cells and large clumps of Gram-positive cocci. Culture of the pus gave a profuse pure growth of coagulase-positive *Staph. aureus*. The antibiotic sensitivity was determined by the disk method. The organism was found to be resistant to penicillin, streptomycin, and sulphadimidine, but sensitive to chloramphenicol, and, when tested on a nutrient agar plate at *p*H 5.8, highly sensitive to "aureomycin."

Tube titrations with these antibiotics were later performed, and the organism was found to be resistant to 100 units of penicillin per ml. and to 100 μg. of streptomycin per ml. It was sensitive to chloramphenicol in a concentration of 2.5 μg. per ml. and to aureomycin in a concentration of as little as 0.01 μg. per ml. This test was performed in nutrient broth at *p*H 6.8 and the results were read turbidimetrically (Anderson, 1951). Lumbar punctures performed as a routine on each post-operative day showed a pleocytosis which reached 1,100 per c.mm. on the third day, a figure which is considerably higher than that generally seen. By the eighth day, however, the level had fallen to 80 cells, which was judged to be within the usual limits for a post-operative count. It was therefore considered on clinical evidence that the patient was not suffering from an incipient meningitis.

On the seventh post-operative day, in view of the antibiotic spectrum of the infecting organism, the patient was given aureomycin, 750 mg. six-hourly, by mouth. High cerebrospinal fluid pressures necessitated lumbar punctures twice daily. During the succeeding week the general condition improved and the discharge from the incision became serous and finally ceased on February 28. The cytology of the lumbar cerebrospinal fluid remained within the usual post-operative limits.

On the 16th post-operative day, after some increase in pyrexia, the patient developed a collection of blood-stained fluid deep to the skin flap. This required daily aspiration over the course of four days. Direct films showed masses of Gram-positive cocci, and cultures yielded a pure growth of coagulase-positive *Staph. aureus*.

On the 18th post-operative day the patient presented definite signs of meningitis, and the lumbar cerebrospinal fluid was now turbid, containing 290 leucocytes per c.mm., with 90% polymorphonuclear cells. Direct films of the centrifuged deposit showed several groups of extracellular Gram-positive cocci. Culture yielded a scanty growth of coagulase-positive *Staph. aureus*. This organism proved to have the same antibiotic spectrum as the coccus isolated from the wound infection. Thus the patient had developed a meningeal infection despite the fact that he had been given maximal oral doses of aureomycin for 12 days. Subjectively, he complained of increased headache and drowsiness, and examination revealed some dysarthria in addition to neck rigidity, but no Kernigism. The following day it was decided to give chloramphenicol by mouth in doses of 1 g. six-hourly, increasing in 48 hours to 2 g. six-hourly. On the succeeding three days the leucocyte count remained high in the lumbar fluid, and the infecting organism was still seen in Gram films of the centrifuged deposit. In view of this grave situation it was decided to try to increase the concentration of chloramphenicol in the cerebrospinal fluid by intrathecal administration.

On the 23rd post-operative day 100 μg. of chloramphenicol in 1 ml. of sterile distilled water was cautiously given intrathecally; this was repeated on the following day. At the same time 200 μg. was injected into the collection of cerebrospinal fluid deep to the scalp flap. These injections were well tolerated. The considerable nausea experienced by the patient at this stage was thought to be due to the large dosage of aureomycin. The intrathecal chloramphenicol was increased gradually until a maximum of 750 μg. was reached after 19 days. The cell counts in the lumbar fluid and the chloramphenicol levels during treatment are shown in Fig. 1 and the Table. The patient gradually improved, apart from an increase in cells on the 35th post-operative day which may have been due to an escape of infective material

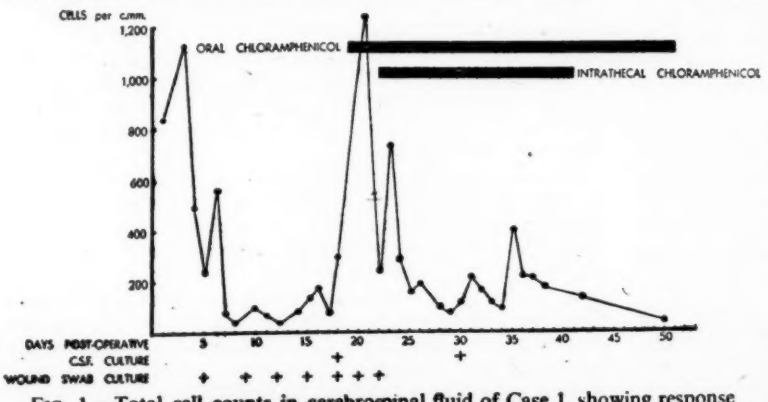

FIG. 1.—Total cell counts in cerebrospinal fluid of Case 1, showing response to chloramphenicol therapy.

Table Showing Chloramphenicol Levels in Cerebrospinal Fluids Related to Daily Intrathecal Dosage

Case 1			Case 2		
Days Post-operative	Daily Intrathecal Dose in μg.	Cerebrospinal Fluid Levels in μg. per ml.	Days Post-operative	Daily Intrathecal Dose in μg.	Cerebrospinal Fluid Levels in μg. per ml.
23	100		14	600	
24	100		15	600	
25	400		16	600	40
26	400		17	700	40
27	400	10	18	700	
28	400		19	750	
29	400		20	—	20
30	400	10			
31	400				
32	400				
33	400	20			
34	500	20			
35	500	20			
36	600	30			
37	600				
38	700				
39	700				
40	700				
41	750	40			

from a focus deep to the flap, although at this time there was no collection requiring aspiration.

One positive culture was obtained from the lumbar fluid on the 30th post-operative day, but all subsequent cultures were sterile. Aureomycin was discontinued owing to severe nausea.

Intrathecal chloramphenicol was discontinued on the 41st post-operative day, after 19 days of treatment, but oral therapy was continued until April 6. The cerebrospinal fluid cell counts fell gradually to normal and the patient's general condition was much improved. He was allowed up, and examination six weeks after the cessation of all treatment showed him to be symptom-free.

Methods

Pure crystalline chloramphenicol was used for the preparation of intrathecal solutions. It must be emphasized that only the pure substance should be employed for intrathecal use in order to avoid the introduction of foreign material and also to ensure accuracy in preparing the solutions. The drug was dissolved in distilled water to give a final concentration of 100 μg. per ml. This was dispensed in ampoules of 1-ml. and 5-ml. amounts. These solutions were subsequently compared with solutions which had not been autoclaved. Each was titrated against the patient's organism, and there was no detectable loss of potency after sterilization in the autoclave. The seven chloramphenicol assays on the cerebrospinal fluid were carried out on specimens taken immediately before the next intrathecal injection. Unit volumes of 1 ml. were employed, making doubling dilutions with nutrient broth. A six-hour broth culture of the staphylococcus isolated from the patient was employed throughout as a test organism, 0.02 ml. being added to each tube from a dropping pipette. Control titrations with known chloramphenicol concentrations were set up in each case.

The first assay was performed when the patient was still receiving aureomycin by mouth, and was therefore complicated by the possible presence of this antibiotic in the cerebrospinal fluid. In view of the relatively high sensitivity of the test organism to aureomycin (0.01 μg. per ml.), and the instability of that antibiotic to heat, it was felt that a combined assay might be attempted. One sample of fluid was titrated in the normal way, whilst a second sample was boiled and cooled before titration. It was thought that this treatment would destroy any aureomycin present, whilst leaving the extremely stable chloramphenicol unchanged. In reading the aureomycin titration it was necessary to make the somewhat unwarrantable assumption that no synergistic action existed between the two antibiotics. The approximate levels so obtained were 0.64 μg. of aureomycin per ml. and 10 μg. of chloramphenicol per ml. After this assay, aureomycin was discontinued, and subsequent estimations were uncomplicated by the presence of two antibiotics.

Case 2

A man aged 47 was admitted for exploration of an acoustic neuroma which was completely removed by an occipital approach on March 16. He subsequently made satisfactory progress, his total cerebrospinal fluid cell count being consistently below 100 per c.mm.

On the thirteenth post-operative day the space deep to the skin flap was aspirated because loculation of cerebrospinal fluid in that site was suspected. The fluid was clear

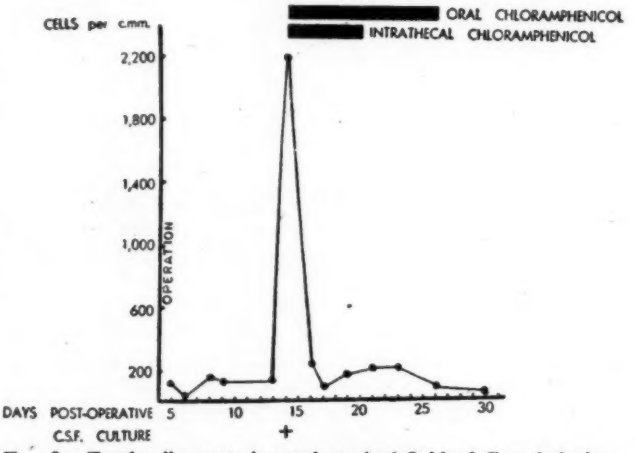

FIG. 2.—Total cell counts in cerebrospinal fluid of Case 2 during chloramphenicol therapy.

and contained 59 leucocytes. Overnight the patient complained of increasing headache and nausea, and his temperature rose steeply to 101° F. (38.3° C.). Lumbar puncture now showed a frankly purulent fluid containing 2,200 leucocytes per c.mm. (Fig. 2). The patient had developed a pyogenic meningitis within 12 hours of aspiration. As the nature of the infecting organism was at that time unknown, treatment with penicillin was begun at once, 500,000 units being administered intramuscularly six-hourly, and 40,000 units injected intrathecally. Immediate examination of the fluid showed large numbers of pus cells and several clumps of extracellular Gram-positive cocci. After 18 hours' incubation, cultures on blood agar yielded a moderate growth of coagulase-positive *Staph. aureus*. In order to provide information about the antibiotic sensitivity at the earliest possible moment, a thick lawn plate was prepared with the appropriate disks and examined by reflected light at the end of six hours' incubation. At this time it was possible to report that the organism was resistant to penicillin and streptomycin, but sensitive to chloramphenicol. Further incubation and tube titrations subsequently confirmed these findings.

All penicillin therapy was immediately discontinued, and, in view of the failure to eradicate the organism in the previous patient with oral aureomycin, it was decided to treat the case with large doses of chloramphenicol, both orally and intrathecally. The patient was accordingly given 2 g. six-hourly by mouth and 600 μg. intrathecally daily, rising to 750 μg. on the sixth day. Within 24 hours there was a marked symptomatic improvement: headache disappeared, and the patient was no longer nauseated or drowsy. Within 72 hours the cell count in the lumbar fluid had fallen to 75 per c.mm. (Fig. 2). By this time

the patient was symptomless and was, in fact, making persistent demands for permission to get up. Intrathecal chloramphenicol was discontinued after six days, and oral therapy after 12 days. The results of three assays performed on the lumbar fluid are shown in the Table. The patient maintained uninterrupted progress and was allowed to get up.

Discussion

It is difficult to explain why Case 1 developed meningitis while receiving full doses of aureomycin by mouth. The infecting organism was shown to be markedly sensitive, and the isolated assay performed while the patient was still taking the drug suggested an adequate concentration to be present in the cerebrospinal fluid. Two possible explanations present themselves. First, it seems likely that the cerebrospinal fluid was subjected to repeated and heavy contamination from the collection of infected fluid deep to the operation flap. This is supported by the findings of numerous cocci in Gram films prepared from several samples of fluid, and also by the isolated positive culture and cell peaks seen in Fig. 1, all of which suggest repeated contamination. Secondly, aureomycin is reported to reach the cerebrospinal fluid in relatively small concentrations.

Werner *et al.* (1950), investigating five patients receiving aureomycin by mouth, were unable to detect the antibiotic in the cerebrospinal fluid. Even with serum concentrations of 7.6 μg. per ml. Bryer *et al.* (1948), working with dogs, failed to detect any measurable amounts in the spinal fluid after parenteral administration. However, Harned *et al.* (1948) found that intravenous administration in dogs resulted in levels up to 0.8 μg. per ml. Owing to the fact that solutions of aureomycin have a final *p*H of 4.5 this antibiotic has so far been considered unsuitable for intrathecal use. Spinal fluid concentrations in patients treated with oral chloramphenicol seem to be more encouraging. Ross *et al.* (1949) have shown that 30% to 50% of chloramphenicol present in the blood may appear in the spinal fluid. Two hours after an oral dose of 3 g. one might therefore expect levels between 14 and 24 μg. per ml. to be present.

In Case 1, at the beginning of intrathecal treatment, 10 μg. per ml. was present in the fluid, the level rising gradually with increasing dosage to a maximum of 40 μg. per ml. In Case 2, in which a large initial intrathecal dose was given, the first estimation showed 40 μg. per ml. to be present, and this fell abruptly to 20 μg. per ml. within 24 hours of stopping intrathecal chloramphenicol, although oral administration was continued. The response to treatment was immediate and spectacular, doubtless owing to the high spinal fluid levels achieved at the onset of meningitis, and also to the fact that this case was not complicated by loculated infected fluid. Both cases indicate that maximal titres in the cerebrospinal fluid were not achieved by oral dosage alone.

It would appear, therefore, that an intrathecal dosage of 750 μg. daily, in combination with oral administration, is capable of rapidly raising the cerebrospinal fluid level to a figure in the region of 40 μg. per ml. Such dosage is well tolerated, and to date there have been no undesirable effects.

Summary

Two cases of staphylococcal meningitis resistant to penicillin and streptomycin are described.

Possible reasons for failure to control the infection with aureomycin in Case 1 are examined, and the methods and results of treatment with intrathecal chloramphenicol are discussed.

We are indebted to Mr. Murray Falconer for permission to publish the details of these cases, and to Professor R. Knox for advice and encouragement during the bacteriological investigations. Our thanks are also due to the Department of Clinical Pathology, Guy's Hospital, for giving us details of the cell counts and protein estimations on the fluids, and for their co-operation in other ways; also to Parke, Davis and Co., Middlesex, for supplies of crystalline chloramphenicol.

ADDENDUM.—Since the preparation of our paper, chloramphenicol has been introduced into the lumbar theca in doses as high as 3 mg. without undesirable results. Where intrathecal therapy has been continued for a week or more, two side-effects have been noted in patients so treated.

1. Depression with tearfulness has been seen in all patients. Some have occasionally responded to lumbar puncture and clinical examination with outbursts of weeping.

2. Where a cerebellar tremor has been present due to a pre-existing lesion or to operative interference, this tremor has been markedly accentuated by intrathecal chloramphenicol.

Both these side-effects have disappeared with the cessation of intrathecal therapy.

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Medical Memorandum

Calcification of the Peritoneum

While it is not very uncommon to find, on radiographic examination, calcification in the pleura and in the pericardium as a result of past tuberculous infection, empyema, or post-traumatic haematoma, extensive calcification of the peritoneum, as distinct from abdominal glands and tumours, would seem from the literature to be rare enough to warrant publication of the following case.

Case Report

A railway worker aged 15 was examined at his home by a tuberculosis officer on November 22, 1947, because of abdominal swelling of three weeks' duration. He had fallen on his chest and abdomen six weeks before and had developed a swelling in his left groin a fortnight later. He now complained of lassitude, anorexia, diarrhoea, night sweats, and loss of weight. His general condition was poor: he was thin and pale, but had no tachycardia or abnormal signs in the chest. His abdomen was distended, fairly tense, with a few visible veins on the abdominal wall. There was deep tenderness and dullness in the left flank, but no fluid thrill. There was a small left inguinal hernia. Tuberculous peritonitis was diagnosed, and he was placed on a sanatorium waiting-list. He remained at home, however, and from April, 1948, reported at three-monthly intervals to the tuberculosis clinic. A radiograph in April showed no abnormality in the chest.

By September, 1948, the inguinal hernia had disappeared, and by December he was so well that his name was removed from the hospital waiting-list. In March, 1949, he had pain in the right iliac fossa for three days, but by May he was thought to be well enough to start light work. He was examined for national service in September, 1950, and a radiograph then showed "fibrosis in the right apex with a partially calcified focus and calcified root glands and fibrosis in the left upper zone with minimal lesions, almost certainly tuberculous." At this time he was working and was free of symptoms. Weight had increased steadily from 5 st. 9 lb. (35.8 kg.) in April, 1948, to 8 st. (50.8 kg.) in September, 1950.

He was admitted to hospital on November 6, 1950, with 48 hours' history of recurring pain in the right iliac fossa. He showed evidence of acute appendicitis with local resistance and rebound tenderness. At operation the same day,

Straight radiograph of abdomen, showing mottled calcified opacities in the line of the ascending colon.

via a gridiron incision, the peritoneum was seen to be studded with small and large masses of calcified material, both visceral and parietal layers being partially calcified. The appendix was acutely inflamed and its tip was embedded in a calcareous mass, while further calcareous material was adherent to its wall. It was removed in the usual fashion. Two days after operation he developed a pyrexial illness due to infection in a collapsed right lower lobe. This complication cleared satisfactorily, and by December 4 no abnormality was detected at the right base clinically, and *x*-ray films of the chest showed only calcified right hilar glands. He was discharged home on December 10. On February 28, 1951, he was very fit and had resumed his employment.

A straight radiograph of the abdomen showed an appearance not unlike residual barium in the bowel, due to scattered calcified lesions throughout the abdomen, mainly in the line of the large bowel (see Fig.).

Histological Report.—The appendix was 55 mm. long, with greatest diameter 22 mm., including in this an aggregation of firm fibrotic calcified nodules which projected like a bunch of grapes from the serous coat. Microscopically the nodules were composed of dense fibrous tissue, enclosing one or more calcified foci. The fibrous tissue was hyaline and, except at the periphery, was composed of collagen without nuclear structure. The reticulin pattern followed that of the collagen. No giant cells or histiocytes were present. Elastica was present only in association with blood vessels. The appearance of the sections was consistent with a healed tuberculous process.

Biochemical Findings.—Blood urea, 19 mg. per 100 ml.; plasma albumin, 5 g. per 100 ml.; plasma globulin, 3.4 g. per 100 ml. Thymol turbidity test, 3 MacLagan units. Serum calcium, 11.5 mg. per 100 ml.; serum inorganic phosphorus, 3.49 mg. per 100 ml.; serum alkaline phosphatase, 18.1 King–Armstrong units. Urine: Sulkovitch test for calcium excretion normal. The Schlesinger test for urobilin was negative.

Comment

We have been unable to find a description of any similar case in the British or American literature, although the condition does appear to be recognized on the Continent. Hertzler (1921) goes into all aspects of tuberculous peritonitis very fully, but without mentioning calcification. Steinberg (1944) merely mentions that "tubercles [on the peritoneum] may undergo resolution or fibrosis with subsequent calcification or caseation." Widmann *et al.* (1938) discuss, with particular reference to radiology, practical aspects of calcification and ossification in various tissues, but the peritoneum is omitted. Myers (1925) describes a small bony mass at the tip of a chronically inflamed appendix; while Capecchi (1928) describes calcareous ossified concretions, "the result of abortive tuberculous peritonitis." One case of calcification of the peritoneum is reported by Perotti (1931). Bory, Azéma, and Calmet (1946) present two cases with calcified miliary lesions of pleura and peritoneum, while Hultén (1927) describes a case of tuberculous peritonitis followed by calcification in abdomen and pelvis.

We find it difficult to believe that healing of tuberculous lesions and exudate in the peritoneum should be so rarely attended by widespread calcification as the literature and textbooks would suggest. The calcified mottling is easily missed on a routine radiograph, and we venture to hope that this report will help surgeons and radiologists to recognize similar cases.

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The invaliding rate for pulmonary tuberculosis in Gurkhas serving in the British Gurkha Brigade in Malaya is much higher than that for British troops, reports the Army Medical Directorate. It was at one time considered that the Gurkha was not exposed to tuberculosis in Nepal, and in consequence was more susceptible to infection in Malaya, where the incidence in the civil population is high. More recent information has indicated, however, that there is a good deal of tuberculosis in Nepal. The problem is being tackled in two ways. At the Gurkha recruiting depots in India arrangements have been made for all recruits to have a radiograph of the chest, and any intending recruits with evidence of disease or doubtful radiological signs are not enlisted. In order to examine Gurkhas already serving, a fully mobile miniature mass radiography outfit with a team consisting of three radiographers has been dispatched to Malaya and is touring all Gurkha units and training centres. Among 6,463 films 32 open cases and 30 closed cases were found.

Reviews

MICROARTERIOGRAPHY

Microarteriography. By Alfred E. Barclay, O.B.E., M.D., D.Sc.(Hon.)Oxon, D.Sc.(Hon.)Manchester, F.R.C.P., F.F.R., F.A.C.R. (Pp. 102; 46 figures. £1 10s.) Oxford: Blackwell Scientific Publications. 1951.

In this beautiful little book, dedicated to "those who follow after," the late Dr. A. E. Barclay, with a characteristic combination of practical instruction and prophetic imagination, closes his long list of published work. He does this conscious of his approaching end. As a result, in this volume are to be found, among the facts and theories, something of the enthusiasm which inspired his daily work, of the delight with which he tackled and overcame technical problems, and of his conviction of the important part that the scientific approach in radiographic methods can play in the natural sciences.

In a short introductory chapter the author makes the point that radiographic technique provides a means of investigating function and structure with a minimal disturbance to the natural state of the organs and tissues involved, both during life and after death. He describes the development of the research in the Nuffield Institute, Oxford, which was originally inspired by the work of Trueta and Barnes on the vascular effects of crush injuries of the limbs. Spasm in the femoral arteries suggested that impairment of the blood supply to the kidneys might underlie the renal changes found in these injuries, and the application of cinematographic methods to the passage of opaque substances through the kidney strongly suggested that a short-circuiting of the cortex took place. Injection of minute vessels with "neoprene," and, later, microarteriography itself, were used because of the failure to demonstrate the site of the shunt by coarser methods. This section of the book closes with the vision of microarteriography applied more generally to the physiology of the peripheral vascular system.

In the next section the author considers the practical details of the methods used, and he compares and contrasts the technical problems of *x*-ray cinematography, direct and indirect. He then discusses in detail microarteriography itself, and describes the production of low-voltage *x*-ray beams, fine-grain emulsions, the mounting of thin slices of tissue without the help of *x*-ray absorbent materials, the radiographic details involved, and, finally, the problems of enlargement of the resulting film.

Dr. R. G. Harrison, of the Anatomy Department of Oxford University, contributes a chapter on the possible contrast media that may be used in this work, with particular reference to the size of particle, toxicity, and the drawbacks that were encountered. Barclay's section of the book ends with a fascinating chapter on the applications of microradiography, in which there are some first-class illustrations. That of the complete renal structure from the cortex to the tip of a papilla, magnified 70 times on an illustration 3 ft. long, is as original as it is effective. The text describing the interpretation of these pictures is a most impressive example of the author's simultaneous attention to detail and breadth of vision.

Two small contributions by Dr. R. G. Harrison on the blood supply of the testis and by Mr. D. Leatherdale on the applications of this work to botany complete the book, except for the epilogue, which is Barclay's plea for co-operation between clinician and research worker in the tackling of physiological problems.

The whole is a self-effacing attempt, so typical of the author, to make available to others the results of his careful and extensive work. Time has yet to prove the value of this technique, and at the moment its applications would appear to be many and varied. The development and demonstration of its potentialities are major achievements in research, and because of this alone this little book may well become a classic.

C. J. HODSON.

THE ENDOCRINE GLANDS

Endocrine Diagnosis. By H. Ucko, M.D. (Pp. 513; 84 figures. £2 2s.) London: Staples Press. 1951.

This book has the advantage of being "the outcome of a life-long interest in endocrinology" and is "primarily intended for the clinician." In the first part (305 pages), on the differential diagnosis of endocrine symptoms and signs, the author attempts to be too theoretically comprehensive, at least in the tabulated classifications, and a good deal of physiology sometimes obtrudes rather than clarifies. Yet he gives much valuable information, with references, on such subjects as hyperostosis frontalis interna and the normal range of measurements of the sella turcica, measured radiographically. Such unusual terms as hypomastia and amastia are introduced in the breast section.

The plan leaves for Part II fewer than 200 pages for a consideration of diseases of the endocrine glands under separate headings for each gland, and it is said to be a synthesis of information gained in the first half. Of thyrotoxicosis the author states that "in about 50% of cases a brown pigmentation of the skin develops, which may affect the whole body or be confined to the lids, limbs, hands or dermal folds." This is an unusual clinical experience. The author indicates his appreciation of mineral metabolism studies by referring to the depletion of potassium in diabetic ketosis. He does not forget endocrinopathies in children, and points out that convulsions in infants and children may be due to hyperinsulinism. The section on the adrenal steroids is comprehensive in a short space, and Cushing's syndrome is effectively discussed. There are some 80 illustrations, and most are good.

This is a useful book, but it could be very much better if either the scheme of presentation in the first half or that in the second half could be applied to the whole book, and if the author could be more ruthless in keeping to his important title "Endocrine Diagnosis," with the emphasis on the diagnosis.

S. LEONARD SIMPSON.

SURGERY OF TRAUMA

A Field Surgery Pocket Book (Revised). Memoranda Mainly Based on Experience in the 1939–45 War. Prepared under the direction of the Director-General of Army Medical Services. (Pp. 188. 4s.) London: H.M. Stationery Office. 1950.

The new edition of this book is a sound compendium of the surgery of trauma from first-aid to rehabilitation. It is to be recommended strongly both to the registrar and to the casualty officer in civil hospitals as well as to all those concerned in the repair of wounds in war. The method of the book is perhaps dictatorial, as might be expected in a Service manual; but the younger

generation of surgeons tends to welcome direction and dictatorship. Moreover, the essentials of early surgical treatment in war, so important to the recovery of the patient and the man-power of the Army, do not permit of initiative, especially on the part of the tyro in war surgery.

The recommendation that, when tying the main artery after injury, the vein should be left intact is contrary to the experience and practice of both Makins and Subbotich, and indeed to my own and that of a good many experienced surgeons, who find that the chance of the limb surviving without gangrene is greater if, after the tying of the main artery, the limb is elevated for a few minutes to drain it of blood and the main vein is then ligated. The section on surgery in the field is sound and to the point, but possibly more emphasis might have been laid on the essential surgery of wound cleansing and excision as against the use of antibiotics and chemotherapy, which are surely no more than valuable adjuncts to efficient and early wound excision. The sections on abdominal and abdomino-thoracic wounds are sound and practical, as are those on plaster, transfusion, wound infections, joints, amputations, and wounds of hands. The plans for the lay-out of both operating units and theatres are practical. I am glad to see that they do not envisage the use of field surgical units (apart from exceptional circumstances) further forward than the casualty clearing station, and that two or more must be employed together. Possibly this raises the question of the future establishment of field surgical and transfusion units being increased to include two teams. The special departments are briefly but adequately described, as is surgery at the base and rehabilitation.

Like all the Army publications this is sound, concise, and strongly to be recommended as a practical manual which can be carried in the pocket, and it is a most valuable aid to those dealing with casualties in any walk of life.

P. H. MITCHINER.

GOETHE AS SCIENTIST

Der Naturforscher Goethe. Report of Rudolph Virchow Medical Society, 1949. By Professor Bruno Kisch. (Pp. 78; illustrated. No price.) New York: Rudolph Virchow Medical Society. 1949.

In the *Encyclopaedia Britannica* (1929) Goethe's "scientific studies and discoveries" are mentioned as possessing "only a historical interest." This view is not tenable. Goethe's importance as the founder of modern morphology has received ever-growing recognition during the last thirty or forty years. Even his views on the nature of colour, long regarded as curiosities, are now taken seriously.

Goethe was not concerned with the origins of species. His archetypal plant, or *Urpflanze*, was not an ancestral organism from which existing species have "descended." It was the "ground-plan," as it were, according to which every plant develops organically. It was not a "type" that had a tangible existence, nor was it a theoretical construction. It was an immanent reality that could be seen by the "inner eye."

The question that matters is not so much, "Was Goethe right and Darwin or Newton wrong?" (or vice versa) as, "Do Goethe's views on morphology and optics enrich our knowledge to-day?" The answer is that they certainly do. One of the most recent—and most important—contributions to the study of plant morphology, Agnes Arber's *Natural Philosophy of Plant Form* (1951) is deeply rooted in the Goethean conception. In his *Wandlungen in den Grundlagen der Wissenschaft*, the eminent physicist Heisenberg affirms the importance of Goethe's views on optics, with the qualification that Goethe did not go far enough in his opposition to Newton.

This little book issued by the Rudolph Virchow Medical Society is a significant tribute to Goethe as a scientist. It contains several addresses of exceptional merit. Otto Meyerhof's observations (in German) on Goethe's method of inquiry into nature (*Naturforschung*) give a balanced and penetrating account of Goethe's achievement and its importance in our own generation.

F. A. VOIGT.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

A Short Textbook of Midwifery. By G. F. Gibberd, M.B., M.S., F.R.C.S., F.R.C.O.G. 5th ed. (Pp. 576. 25s.) London: J. and A. Churchill. 1951.

European B.C.G. Programmes. Conference of the International Tuberculosis Campaign. (Pp. 333. 7s. 6d.) London: William Heinemann. 1951.

Second Annual Report of the International Tuberculosis Campaign. (Pp. 334. 7s. 6d.) London: William Heinemann. 1951.

Aids to Anatomy. By R. J. Last, M.B., B.S., F.R.C.S. 11th ed. (Pp. 379. 7s. 6d.) London: Baillière, Tindall and Cox. 1951.

The Sober Truth. By L. Williams, M.R.C.S., L.R.C.P. (Pp. 63. 6s.) Leicester: Edgar Backus. 1951.

Medicine of the Year 1951. Edited by J. B. Youmans, M.D. (Pp. 298. 40s.) London: J. B. Lippincott. 1951.

William Davidson of Aberdeen. Tercentenary Memorial Lecture by J. Read, Ph.D., M.A., Sc.D., F.R.S. (Pp. 32. No price.) Aberdeen: The University Press. 1951.

Laughs With the Medicos. Compiled by S. Evelyn Thomas. (Pp. 64. 1s. 6d.) London: S. Evelyn Thomas. 1951.

Gynaecological Endocrinology. By P. M. F. Bishop, D.M. 2nd ed. (Pp. 132. 12s.) Edinburgh: E. and S. Livingstone. 1951.

Tumors of the Adrenal. By H. T. Karsner, M.D. (Pp. 60. No price.) Washington, 25: Armed Forces Institute of Pathology. 1951.

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Annual Review of Medicine. Edited by W. C. Cutting. Vol. 2. (Pp. 485. $6.) Stanford, California: Annual Reviews, Inc. 1951.

Tomorrow's Horizon in Public Health. Transactions of the 1950 Conference of the Public Health Association of New York City. (Pp. 109. $1.) New York: Public Health Association of New York City. 1950.

Sensibilitätsschema (Second edition. M. 4.80 each. Stuttgart: George Thieme), by Professor K. Hansen, consists of two blocks, each of 50 sheets, containing outline diagrams of the human body. On one block the presumed cutaneous distribution of the spinal segments is indicated, and on the other the distribution of the peripheral nerves, one side of the diagram being left blank so that sensory abnormalities in individual patients may be indicated. Most physicians would prefer blank sensory charts on which to indicate areas of sensory abnormality.

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SKIN HOMOGRAFTS IN CLINICAL PRACTICE

Two new papers on homografts (grafts from one individual to another of the same species) are published in this issue, and more than twenty have appeared in British and American journals during the past eighteen months. The majority are on the grafting of skin, though Dempster in his Arris and Gale lecture is no less concerned with the transplantation of kidneys. Evidently there has been a big revival of interest in a problem which biologists and surgeons have been worrying at for forty years. The literature that embodies the history of this work has just been collated and reviewed by Rogers.[1]

Because they give evidence of a very fine-grained genetic polymorphism among human beings, and of the inheritance of intimately gene-controlled differences, homografts interest biologists for reasons quite apart from the possibility of their clinical use. Billingham and Medawar's[2] recent synopsis of the technique of experimental grafting (which includes the methods used for handling epidermal cell suspensions) may help to persuade other biologists into this field of research. But the time has now surely come to make a draft statement of how surgeons may find it best to use skin homografts in clinical practice—if there is a good case for using them at all. That there is *some* such case is certain, for plastic surgeons do indeed sometimes use skin homografts as living dressings for injuries entailing extensive loss of skin. The surgeon normally expects to replace such homografts in due course by permanent grafts of the patient's own skin. The least to be hoped for from modern investigations is that this definitive grafting should be done at a time decided on by the surgeon, and not by the importunities of an immunological reaction.

Suppose, then, that skin homografts are to be used and that, failing immediate donors, there is sufficient skin in store. (Storage presents no particular difficulty.[3]) There is a theoretical case, amply borne out by experimental practice, for using grafts from a variety of donors rather than from a single one[4 5]; and there is as yet no evidence that uniformity of blood groups is of practical importance. How may the skin best be used? If the surgeon proposes to replace his homografts by autografts there is clearly no point in using anything but split thickness grafts providing complete cover for any part of the skin defect that has not been made good by autografts, for pinch grafts and postage-stamp grafts are acknowledged makeshifts, designed only to eke out an exiguous ration of the patient's own skin. If on the other hand the plastic surgeon is hoping to make use of the longer enduring collagenous dermis of his homografts, and to persuade native skin epithelium to grow over and re-colonize it, then it will be desirable to lay autografts and homografts in alternating contiguous strips, as Mowlem has advised. In either event, the total "dosage" of foreign skin will be high. There is clear evidence from rabbits,[4 6] and particularly from guinea-pigs,[7] that this will curtail its survival; but the "dosage effect" is weak over the range of dosages that would be used in clinical practice, and both Dempster and Rogers[1] believe it to be of little or no practical import. A more important precept is that all the homografting that is to be done should be done on one occasion. In rabbits,[4 6 8] guinea-pigs,[7] and mice, the reaction provoked by a first homograft will curtail the life of a second transplant from the same donor on a later occasion. The evidence that this is true of human beings is less secure but far from negligible.[9 13]

The adoption of these precepts may help to rationalize the surgery of skin repair by homografts, but it will not prolong the life of foreign skin. This is the major problem. Dempster, Lennox, and Boag[10] have shown that total body irradiation prolongs the life of skin homografts in rabbits, but, as Dempster says, there is no clear evidence that homografts ever become permanently acclimatized to their hosts even when caused long to outstay their normal welcome. (Some of the Woodruffs's[11] observations on thyroid homografts in the anterior chamber of the eye do, however, give promise of such a possibility.) The systemic administration of cortisone greatly prolongs the life of skin homografts in rabbits,[12] but there are at least two reasons why the clinical import of this fact should

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3 See *British Medical Journal*, 1951, **1**, 1192.
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13 Ellison, E. H., Martin, B. C., Williams, R. D., Clatworthy, H. W., Hamwi G., and Zollinger, R. M., *Ann. Surg.*, 1951, **134**, 495.
14 Weisman, P. A., Quinby, W. C., Wight, A., and Cannon, B., *Ann. Surg.*, 1951, **134**, 506.
15 Cf. the work of Long, D. A., Miles, A. A., and Perry, W. L. M., *Lancet* 1951, **1**, 1085.
16 *Ann. Surg.*, 1951, **134**, 515.

be temperately appraised. The first is that the rabbit is notoriously responsive to cortisone, and that impossibly large doses (from a clinical standpoint) may be needed to produce a comparable effect in man. The second, as Dempster argues, is that the prolonged administration of cortisone (even in moderate doses) which would be required in practice would be certain to have the most undesirable secondary effects. This is not necessarily an obstacle, however, for Billingham, Krohn, and Medawar in the present paper (p. 1049) report that cortisone prolongs the life of skin homografts in rabbits when *locally* applied—even in the technically unsatisfactory form of crystals of cortisone acetate in an aqueous suspension intended for injection. Much smaller dosages of cortisone may therefore now be used. They argue that cortisone so used must be applied to *all* the foreign skin borne by any one patient, because cortisone does not to any clinically important degree protect homografts against an immunity produced beforehand, or concomitantly acquired from untreated grafts. The second objection may then prove to be insubstantial; the first awaits the evidence of further work. Recent clinical trials, so far as they go, somewhat discourage the idea that systemically injected A.C.T.H. and cortisone prolong the life of skin homografts in human beings to a clinically useful degree, if at all. Ellison and his colleagues[13] describe a patient with skin homografts who received 100 mg. cortisone a day: the homografts had sloughed completely within 3½ weeks. Four other such patients received 40–160 mg. A.C.T.H. in subdivided doses daily. The survival times of their homografts ranged from 3 to 7 weeks. One of these patients was repeatedly grafted at one- or two-week intervals, and it is noteworthy that the survival times of the homografts became progressively shorter. Weisman and his colleagues[14] report that skin homografts lasted only 13 days on an 85-year-old female patient who was receiving 60 mg. A.C.T.H. per day; on two other untreated patients, described as "controls" for no reason that is made clear by the text, the homografts survived 50 and 95 days respectively. They state moreover that neither A.C.T.H. nor cortisone prolongs the life of homografts in guinea-pigs and young pigs. In this connexion, it will be interesting to learn of the fate of skin homografts in cortisone-treated guinea-pigs when particular attention is paid to the adequacy of their ascorbic-acid intake.[15]

These two reports, describing between them only one patient who received cortisone during the period of homografting, can hardly be said to refute the possibility that cortisone may be useful in the homoplastic grafting of human beings. The tone of the discussion that followed their delivery[16] was nevertheless unrelievedly pessimistic. It is possible that A.C.T.H. is indeed ineffective, and it is noteworthy that there is no published report that A.C.T.H. prolongs the life of skin homografts in rabbits, in spite of their high susceptibility to the action of cortisone. It may be that A.C.T.H. stimulates the adrenal cortex to produce substances antagonistic to the action of cortisone. At all events, the tendency in some surgical literature to regard A.C.T.H. and cortisone as interchangeable alternatives is much to be deplored.

"OUT, DAMNED SPOT"

Commenting in our correspondence columns (p. 1088) on the present-day fashions of writing scientific papers, Mr. W. Grant Waugh detects in our midst an outbreak of "pseudo-scientific meticulosis." Though not among those epidemic diseases the waxing and waning of which in time are so prettily and clearly set out in the *Journal*'s section of vital statistics, this is clearly no new disease of mankind—though possibly the symptoms may change considerably from one period to another. Maybe in an earlier manifestation the Latin of its victim fell seriously below the best Ciceronian standards, while at all times there is no doubt that purple-hued petechiae have characterized at least some of the afflicted. Among the major signs and symptoms of the present epidemic Mr. Waugh draws attention to "the replacement of humanistic and clinical values by mathematical formulae," the degradation of patients "from human beings to bricks in a column, dots in a field, or tadpoles in a pool," and "the eventual elimination of the responsibility of the doctor to get the individual back to health."

Writers of papers for medical journals would do well to look seriously at Mr. Waugh's charges and to clear themselves—if they can. His accusation of too many graphs and too many dots may fairly be read as too many illegible graphs and too many spurious decimals. Can this charge be entirely refuted? It is more than doubtful. The whole object of a graph, it need hardly be said, is to clarify—to make clearer to the human eye what it finds difficult in detecting in a table of figures. It is, or should be, an axiom that the table of figures itself is almost invariably given (in spite of the editor). Those figures are the basic data, and, given a clear and simple presentation, all who will may read and consider the evidence. The graph is merely an ancillary aid to understanding and interpretation, and if, to quote Mr. Waugh, it is "reminiscent of the blueprint of an oil-refinery," then it has failed wholly in

its purpose. Too many lines crossing one another, too many signs and symbols, too involved a construction of columns and rows, all defeat the eye and the object. Such a graph may, of course, look clear to the author, but he has "grown up" with the data: he overlooks the fact that it is all new to the reader and that it is his duty to help him. Similarly he may make the path of the reader—particularly of the one who is just a shade allergic to the decimal system—more difficult than it really need be. Nine deaths in 35 patients is a perfectly clear statement, and it does not need a table for its presentation. But, though for comparative purposes it may well require a percentage form, there is rarely any point in translating it into 25.7%. "Of whom 26% died" would in almost all circumstances be enough: and often "approximately one-quarter" would serve the purpose.

Another certain way of deterring the would-be reader—and presumably most authors do wish to be read—is the unnecessary introduction of symbols. "If amongst x mice thus treated, p be the number of animals surviving and $x - p$ be the number dying, then the mortality experience is measured by the ratio of $x - p$ to x." This is merely a somewhat long-winded way of saying that the death rate is the number of mice dying in relation to the total number treated—a good way of ensuring that one's major works remain unstudied. Equally there should be no introduction of mathematical methods in a paper directed specifically to the non-mathematically minded *when other methods of proof will suffice*. None of these accusations can, needless to say, be properly levelled against those diagrams which are essential but yet which, to the untrained, may be very difficult to read—for example, graphs drawn on a logarithmic scale—or against the introduction of the whole of the Greek alphabet and mathematical-statistical methods galore when these are really needed for solving a problem. Their introduction can on no account be denied in these circumstances, and Mr. Waugh clearly does not make any attack upon them. It is against the "pseudo-scientific" that he wields his spear. The scientific writer, Mr. Waugh would doubtless agree, might well take to heart the saying that while it does not take a great mind to make simple things complicated it takes a very great mind to make complicated things simple. And if he, the scientific worker, will apply his great mind to it he may find, as Lord Macmillan once said, that "there are few higher intellectual pleasures than success in the task of expressing an argument or a conclusion in just precisely the right language, so that the thought is caught and poised exactly as we would have it. Clear thinking always means clear writing, and clear writing is always good writing."

On his other charges Mr. Waugh would appear to be on much less sure ground. He points out that "since science is mensuration, a sound statistical survey of any particular form of treatment is of importance." That being so—and, indeed, how could it be otherwise?—it is difficult to see how the results of this "sound statistical survey" can be analysed other than by a "sound statistical method" and presented otherwise than in a "sound statistical table," with, if necessary, mathematical formulae. By so doing, in what way are we degrading the patients and shirking our responsibility as doctors to get the individual back to health? The whole essence of the survey is to see whether a new treatment will benefit patients. There appear to be two ways of going to work. We may try it on John Smith and Mary Robinson and report the results—that John Smith got well quickly and Mary Robinson, poor soul, died. We have done our best for both. Or we may try it on 30 John Smiths and 20 Mary Robinsons and report the numbers that lived and died. It is likely that the larger numbers will be found more informative than the smaller. But have we done any less for the 50 than we did for the two? Further, if there be no ethical reasons to forbid—a paramount and overriding proviso—we may contrast the 30 John Smiths and 20 Mary Robinsons with an equal number of men and women not given this new and wholly unproved drug. Wherein have we shirked our duties? In treating patients with unproved remedies we are, whether we like it or not, experimenting on human beings, and a good experiment well reported may be more ethical and entail less shirking of duty than a poor one.

It is idle to say that patients are so different that statistical comparisons are impossible. It is because they are so different that statistical comparisons are essential. Admittedly the statistical trial can only say that *on the average* this treatment will help patients with such-and-such a disease—and never that this treatment will help John Smith or Mary Robinson. But what clinical method of trial and observation can lead to any other result and be specific? It may, perhaps, be argued that even though there is no evidence that a group is benefited by a particular procedure it is always possible that a particular individual was benefited. But if there be many such individuals the group reaction will reveal it, and if there be very few we can fairly say, after a controlled trial, that any benefit given to these few is equally often seen when the special

treatment is withheld and that rapid or astonishing cures appear equally on both sides of the score sheet.

It is also difficult to follow Mr. Waugh's argument that "no statistics can cater for the psychological element in the treatment of disease." Indeed, the very opposite would seem to be the case, that only by the application of a statistical–clinical trial can in fact these elements be controlled. His own example of the patient suffering from rheumatoid arthritis and "cured" with 20 doses of distilled water would seem to prove this. Supposing the patient had been given A.C.T.H. as intended—then here we have a "successful" cure with a new treatment. There is nothing whatever in the "trial" to reveal the fallacy of that conclusion. But take 50 patients and, with their consent, let 25 be given A.C.T.H. and 25 be given distilled water. Will not the psychological factor reveal itself, that equal numbers will recover on hormone and water? This, in effect, was the method of trial of deoxycortone and ascorbic acid adopted by Quin, Mason, and Knowelden.[1] It showed clearly that the "real" treatment had no superiority over normal saline, though both might ease the pain and add to the strength of the individual patient. By what other method than the comparison of group reactions could this elusive psychological factor have so clearly stood revealed? It stands to reason that all this is not to deny that a few exact and often beautifully made individual observations have an equally important part to play. Clearly one observation alone might change the whole outlook on a disease. But observation of the individual and the statistical approach by means of the group are not incompatibilities; and within the clinical trial on the group there is nothing whatever to inhibit the most exact recording of individual reactions.

A COLLEGE OF GENERAL PRACTICE

In a letter to the *Journal* of October 13 Dr. F. M. Rose and Dr. J. H. Hunt made a plea for the formation of a college of general practice, noting that there are colleges of physicians, surgeons, obstetricians and gynaecologists, nurses, midwives, and veterinary surgeons. This suggestion found a ready response in the shape of several letters which appeared in the *Journal* of October 27 and again this week. Dr. Thwaites put it thus: "Broadly, I would say that a College of General Practice should have as its guiding charter the task of seeing to it that general practice becomes, and continues to be, a branch of medicine which will be entered eagerly, practised with satisfaction, and retired from with regret."

Memoranda by Drs. Rose and Hunt[2] also outlined their views on the need for a college in this branch of medicine. In the words of Dr. Rose, "Such a body would be the repository of the traditions and ethics of general practice which otherwise are likely to be lost irretrievably within a generation." He sees the college as concerned with medical education and research in relation to general practice. The collection and publication of suitable papers and surveys would come within its scope, and it would participate in the foundation in medical schools of lectureships and departments of general practice. Both he and Dr. Hunt think that some kind of higher diploma might be awarded. This is a much more debatable proposal and needs careful scrutiny. Many believe that there are already too many diplomas of one kind or another, and the addition of another might well prove to be unnecessary. Learned bodies obtain their membership in two distinct ways and also by a combination of them. The Royal Society, for example, elects its Fellows; the Royal College of Surgeons makes them pass examinations; while the Royal College of Physicians makes doctors pass examinations for Membership and then elects its Fellows. But membership or fellowship of a college of general practice is a problem that will no doubt be studied. It should not be difficult to solve satisfactorily.

Since July, 1948, the discontent of general practitioners over their remuneration has been so widely publicized as to mislead the public into believing that this is the principal, or even the sole, grievance practitioners have about their work in the National Health Service. The eagerness with which the idea of a college has been pursued shows, on the contrary, that the fundamental concern of general practitioners is lest the quality of their work should deteriorate along with their prestige and professional status. As our correspondence columns show, general practitioners above all want to have the fullest opportunity for practising medicine in such a way as will enable them to give of their best to their patients. In this, as in other things, what matters is the setting of high standards and seeking to maintain them. That the existence of a college of general practice would further this end is clearly in the minds of our correspondents. The idea, as is pointed out in a letter this week, is by no means a new one, for it was brought forward in 1845 as an outcome of Sir James Graham's Bill "for the better regulation of medical practice throughout the United Kingdom." In the *Provincial Medical and Surgical Journal* of January 15, 1845 (the forerunner of the *B.M.J.*), there were outlined the principles of "the proposed college of licentiates in medicine and surgery." In this there were to be a council or governing body and a court of examiners. To-day, over 100 years later, the idea of a college

[1] *British Medical Journal*, 1950, 2, 810.

[2] *British Medical Journal Supplement*, October 27, pp. 173 and 175.

is once more mooted. It may be, as Dr. Batten puts it, "a little hard to bring the proposed college down to earth." But, if one is to judge by the volume of support the suggestion has received, it should be examined with the idea of finding reasons for, rather than against, its establishment. If general practitioners are to regain ground they believe they have lost, and if the general practitioner is to become the focal point for the care of the sick, conditions must be changed to make these desirable things possible.

RUPTURE OF THE SPLEEN

Rupture of the spleen is a commoner accident in this country than is generally supposed. It should be deliberately considered as a possibility after any accident where the abdomen or the lower part of the left chest wall has been struck. Such a blow may result from a fall from a tree or wall, over steps or a kerb. Children are especially prone to these accidents. Motorists and cyclists are liable to be flung against objects, cyclists often striking themselves against the handle-bars. People who have been run over or crushed, the inebriated, and the patient with multiple injuries, all warrant special care.

Initial haemorrhage may be profuse and rapidly fatal if untreated. Usually slight to moderate haemorrhage causes a fall in blood pressure, and adequate clotting occurs to control the haemorrhage temporarily. By the time the patient is first seen there may be little in the general appearance to arouse suspicion of the true nature of the injury.

Meteorism is a frequent accompaniment of ruptured spleen and assists diagnosis by giving rise to cardinal physical signs in the abdomen—namely, marked hyperresonance in front over the splenic area due to distension of the stomach and colon, with dullness behind and in the left flank due to blood clot.

In cases where the spleen is the only viscus injured, pain is variable, tenderness slight, the abdomen is soft, and bowel sounds are present. If ribs are fractured, pain is increased and there is often left-sided rigidity. An associated hollow viscus perforation causes general peritonitis with pain, rigidity, and absent bowel sounds.

The management of cases with obvious internal haemorrhage is straightforward. Blood transfusion and early operation are indicated.

Most cases are admitted for observation, and considerable reliance is placed upon the pulse chart, but it is important to realize that pulse rate and blood pressure may remain steady for a long time. In fact, nothing untoward may occur until the patient collapses, often in the lavatory when straining at stool. In other cases fresh haemorrhage is heralded by rising pulse rate and increasing pallor, advancing to air-hunger and collapse. Such disasters can, and should, be prevented by careful re-examination after admission, when the classical physical signs should lead to early operation. Blood transfusion is a wise precaution in all cases diagnosed. At operation haemorrhage can be quickly and effectively controlled by slipping the fingers round the left side of the spleen and grasping the pedicle. Blood and clot may then be cleared out and the spleen removed in a deliberate manner.

SEX REVERSAL

The history of sex reversal, founded on speculative thought, may be judged best by the human passions it has provoked. Hippocrates records how the ancient Eastern people viewed it with superstitious awe, and regarded it as an example of divine will or intervention. The Greeks banished these supernatural ideas, and took a more practical and rational view, although in Sparta monstrous children were destroyed for eugenic reasons. From Roman times right up to the Renaissance sex reversal was considered to be a manifestation of divine anger and a harbinger of national calamity. The reaction was cruel, for to propitiate the gods these unfortunates were put to death. More recent times have accorded these individuals the right to live and the right to choose their own sex, but even to-day the social sense remains offended by their presence as foci of moral depravity, and the male homosexual is still liable to punishment by law.

Contemporary medicine, owing to increased knowledge, is taking a more humane and lenient view. For long it has been hampered by a confusion of unqualified terms. "Hermaphroditism," with its numerous bisexual representations, must be discarded and relegated to the mythical concepts and vivid fancies of poetry, literature, and art. Sex reversal, applicable in a general sense, implies complete reversal with fertility, a phenomenon that may occur in lower animals but is only partial in man. On the other hand the more scientific term "intersexuality" embraces all its manifestations, and may be defined as the appearance of characters proper to one sex in the opposite sex, including physical form, sex development, and behaviour. These characters may be present in any combination and proportion; consequently the variations are endless. Practically, we find the female is far less stable, and her masculinization is much more common than feminization of the male. Although each individual normally has embryonic rudiments and secretes the sex hormone of the opposite sex, we owe to the work of embryologists ideas which lead to marked clarification of the problem. The genetic determination of sex—xx for the female, and xy for the male—has long been known, and the act of fertilization endows the genes with great dynamic power towards rapid cell division of the ovum. The cells possess the capacity not only for organizing themselves, but for directing the growth of other cells, a process accomplished by means of a morphogenetic hormone—perhaps chemically allied to the steroid group. At a later date this control is largely vested in the endocrine system. Should this organising process prove abnormal, then the endocrine glands may modify the original genetic development. For instance, the transient presence of the fuchsin-staining material in the female foetal adrenal cortex (male phase), if strong and

prolonged, may be the latent or immediate cause of adrenal intersexuality.[1]

Turning from cause to effect, the clinical classification becomes simplified if we regard intersexuality as a flaw in the process of normal embryonic development. Indeed, we may regard the perfect normal male and female in effect as the most refined degrees of intersexuality, with several clinical groups between the two. Starting with masculinization of the female, these are post- and pre-pubertal forms of virilism; then the true hermaphrodite with ovo-testes; the intersex with female genitalia and undeveloped testes in the position of the ovaries; finally hypospadias, with varying degrees of testicular development and descent from the abdomen to the scrotum.

All these intermediate groups contain the neuters of no-man's-land; they are difficult to differentiate, except that those of adrenal origin excrete excess of androgens. Surgery is necessary in the adrenal group, and for diagnosis and for plastic repair. Implants of the appropriate sex hormone are becoming increasingly useful. The psyche does not necessarily follow the genetic determination, and when they are opposed psychotherapy is necessary; when it is associated with secondary glandular disturbances it is helped by organotherapy or surgery. When genetic determination is indefinite, treatment should be directed towards the sex of choice.

NOT TOO OLD AT 40

Though a general practitioner—or indeed anyone—is likely to be a wiser man at the age of 40 than he was at 25, some executive councils seem to think otherwise. Sometimes a doctor's age alone has deterred executive councils from appointing him to a vacancy, and according to the Medical Practices Committee one executive council "eliminates without further consideration all candidates above 40 years of age." The difficulties of entering general practice are great enough without a candidate's being penalized for his age and spurned for the experience that goes with it. If this kind of policy ever became widespread it would be almost impossible for a middle-aged doctor to start practising in a new area.

In response to the discovery that this was going on, the Medical Practices Committee recently sent a letter, from which the above quotation is taken, to executive councils, drawing attention to a number of facts that should already have been uppermost in the minds of the people responsible for the local administration of general practice. As it points out, there are good doctors aged 60–65 or less who have no regular employment and no prospect in such a system of obtaining it. Despite repeated applications for advertised vacancies they fail to obtain a place on any short-list. Many of the vacancies have been of moderate size and well within the capacity of such doctors. There are also elderly doctors in large industrial practices looking for modest vacancies in more pleasant areas. They are entitled to some consideration in their efforts to go to less strenuous practices, as men in their position often did before the Health Service started. The large practices they leave then become available for younger men. It is to be hoped that the offending executive councils will take heed of the Medical Practices Committee's letter and cease to send doctors begging merely because they have attained middle age.

[1] Broster, L. R., *et al.*, *The Adrenal Cortex and Intersexuality*, 1938, London.

DURHAM CLOSED SHOP

The closed shop policy has sneaked in again at Durham, this time as a disingenuous footnote whose effect is to cast doubt on the assurances formerly given. The county council now requires applications for extension of sick leave with pay to be made through the employee's trade union or professional organization.[2] The result is that a doctor who is not a member of such an organization cannot apply for this benefit, and the county council's obvious intention is to continue imposing its closed shop policy on doctors indirectly. In justification the county council contends that payments of salary on extension of sick leave are *ex gratia*, and that it can therefore prescribe the manner in which the applications should be submitted.

Last August the county council gave an undertaking[3] that doctors applying for its posts would not be questioned about membership of professional organizations or trade unions, and that any information received about such membership would not be taken into consideration when an appointment was made. Because of this assurance the ban on the county council's advertisements in this *Journal* was lifted. The spirit underlying the assurance was evidently interpreted too liberally. The B.M.A. assumed that an agreement had been achieved whereby doctors were not to be subjected to requirements which, however established in other types of work, are as alien to the traditions of medicine as they are detrimental to its practice to-day. It is now apparent that the doctrinaire rigidity of the council's policy contrasts notably with the tactical fluidity with which it tries to execute it.

The desire for a "closed shop" came from the workers themselves in order to gain bargaining strength when negotiating with employers. Now we find an employing body trying to impose it from above, not merely on employees who may agree with their employers on the need for it but on other employees who see in the policy an encroachment on their professional liberty. It is a policy both unnecessary to the well-being of professional men and injurious to the relationship between profession and public. The B.M.A. has never wanted doctors to be compelled to join it or any organization and will resist all attempts to make them do so. A deputation is to explain the Association's views to Durham, and it is to be hoped that they will find a receptive audience.

Captain the Rt. Hon. Harry F. C. Crookshank, Conservative M.P. for Gainsborough, was appointed Minister of Health on October 30. He is 58, and has represented Gainsborough since 1924. His last office was that of Postmaster-General in 1943–5.

[2] See *Supplement*, p. 189. [3] *British Medical Journal*, August 18, p. 410.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

SEBORRHOEIC DERMATITIS AND ACNE VULGARIS

BY

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A seborrhoeic subject is born with a skin that has a tendency to produce an excess of sebum, and in some cases this is complicated by a periodic diminution of its resistance to infection by bacteria, yeasts, and fungi. Such a skin is not necessarily in itself pathological. The seborrhoeic state is a constitutional trait conditioned by the endocrine make-up of the patient under genetic influences.

Many seborrhoeic subjects can be recognized by the dirty yellow or grey and greasy skin of the face. The pilosebaceous orifices are patulous, particularly over the alae nasi, temples, and concha of the ear. The patient may not claim that his skin is greasy and he may even complain that it is too "dry." This is due to the presence of fine greasy scales in the nasolabial folds and sometimes over most of the facial skin. Similar scales are found on the eyebrows, around many eyelashes, over the temples, and on the hairy areas of the chest, the axillae, and the pubes. There is nearly always some pityriasis capitis (dandruff) or scurf.

The seborrhoeic state is usually the background of seborrhoeic dermatitis; acne vulgaris; folliculitis; sycosis of the beard, moustache, and nape of the neck; furunculosis; and intertrigo. Acne necrotica and rosacea frequently have a similar background.

Predisposing Factors

Although there is probably no single cause, certain initiating and perpetuating factors are recognized, and an analysis of the many possible causes must be considered in every case. External conditions which augment the seborrhoeic state are the inadequate removal of sebum by washing, retention of sebum by wearing wool and flannel garments, and infrequent change of clothing. Important internal factors are lack of exercise and a diet containing more carbohydrate than is required for normal metabolism. The presence of an acute or chronic anxiety state is a very important factor. Shyness, frustration, an inferiority complex, or a tendency to make mountains out of molehills all play an important part in the aetiology.*

The influence of the hormones on the seborrhoeic state, and particularly on acne vulgaris, has been stressed by H. W. Barber, who regards both as the expression of epidermal stimulation by androgens. It is interesting that testosterone given in large doses will induce greasiness of the skin, comedones, papules, and pustules in women, and spontaneous recovery of the skin follows when this hormone is stopped. Acne in young women often shows a premenstrual exacerbation, and this may be relieved by stilboestrol therapy.

Seborrhoeic subjects are prone to develop eruptions from halogens. The bromide in a sedative mixture or iodide in a cough mixture or gargle may provoke an outbreak of papules and pustules.

*Wittkower, E., *Brit. J. Derm. Syph.*, 1951, **63**, 214.

Eventually there is a breakdown in the normal defences against micro-organisms. The *Pityrosporum ovale*, the *Corynebacterium acnes*, and the *Micrococcus cutis communis*, which are normal inhabitants of the skin, may induce inflammatory processes in those areas where there is the maximum amount of sebum. *Staphylococcus aureus*, *Staphylococcus albus*, and *Staphylococcus citreus* may also be responsible for folliculitis, boils, and certain cases of pustular acne. It is important to remember that the staphylococcus frequently inhabits the vestibule of the nose and is thus easily disseminated over the upper lip and beard areas, either directly or by means of a handkerchief. This is of particular importance in cases of sycosis barbae and folliculitis of the upper lip, chin, and neck. It is difficult to assess the part played by a focus of bacterial infection, but there is no doubt that many patients improve when the focus is removed by radical treatment. Operations which entail an unusual strain on the epithelium or glands of the skin, such as the frequent or prolonged contact with oil, paraffin, or other chemical substances, are detrimental to seborrhoeic subjects. Profuse sweating such as one would see in a heavily laden soldier in the Tropics also predisposes towards a seborrhoeic dermatitis. In the armed Forces it may be prudent to exclude from tropical service a seborrhoeic subject who has had one acute attack.

Clinical Features of Seborrhoeic Dermatitis

In the development of seborrhoeic dermatitis one can discern five different grades of severity.

1. An almost asymptomatic abnormal greasiness with greasy scales in some places.

2. Irritation and itching associated with such scaling and greasiness, relieved by washing, appropriate clothing, and a healthy regime.

3. Sensitization to the normal skin saprophytes or possibly to drugs used in treatment, resulting in erythema, exudation, and a slight crusting—an actual dermatosis. Patches of

FIG. 1.—Seborrhoeic dermatitis in a boy, showing retro-auricular fissures. (With acknowledgment to Dr. W. J. O'Donovan.)

scales behind the ears or within the external auditory meatus are present, and may be associated with painful splits or fissures (Fig. 1). Yellowish red groups of papules surrounding the hair follicles and covered with scales are seen over the sternum and in the interscapular region (Fig. 2). Confluence tends to occur, producing greasy, yellowish red, or sometimes scaling lesions, often compared with the petals of a flower.

4. Secondary infection by pathogenic organisms—sometimes with a yeast or fungus infection. In severe cases secondary pathogenic coccal infection is superimposed, producing a marked exudation and "impetiginization" (Fig. 3). Scales are replaced by crusts and the regional lymphatic glands may also be enlarged and tender.

5. A widespread generalized sensitization with all the above features and most of the body involved. The patient may become incapacitated by extreme discomfort from oozing of the skin, matting of the hair, and deafness from painful swollen ears with retro-auricular fissures. Boils in the auditory meatus, axillae, neck, and buttocks add to his troubles. Infection of the apocrine sweat glands leads to deep abscesses in the axillae and ano-genital regions. Such a severe case may have an atopic background with a familial tendency to asthma, eczema, and hay-fever.

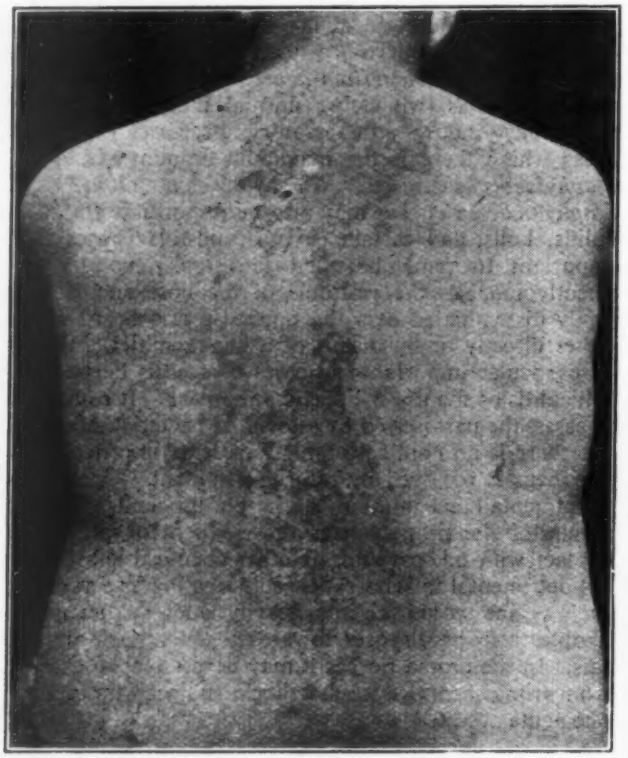


FIG. 2.—Seborrhoeic dermatitis of the back. (With acknowledgment to Dr. R. M. B. MacKenna.)

FIG. 3.—Seborrhoeic dermatitis of the axilla.

Clinical Variants

Infantile seborrhoeic dermatitis often occurs in the first few months of life as a dry crusting of the scalp. Yellowish patches with fine scaling may be seen on the body, and the flexures tend to become red and may ooze.

Folliculitis barbae (Fig. 4) may occur in seborrhoeic subjects with little evidence of frank seborrhoeic dermatitis elsewhere. It is important to recognize this back-

FIG. 4.—Folliculitis barbae in a seborrhoeic subject.

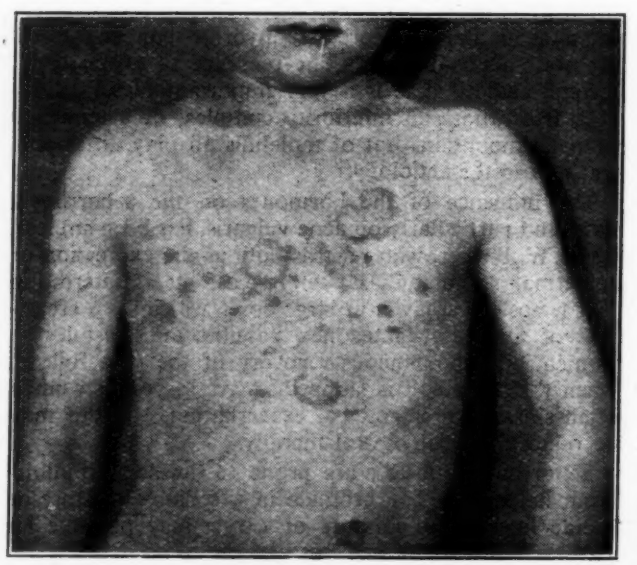


FIG. 5.—Circinate seborrhoeic lesions on a boy's chest. (With acknowledgment to Dr. W. J. O'Donovan.)

ground in cases in which diffuse coccal dermatitis with "impetiginization" has been superimposed on a seborrhoeic state.

Discoid lesions (Fig. 5), varying in size from 1 to 5 cm. across and covered with the characteristic greasy scales simulating psoriasis, chronic localized eczema, or ringworm may occur on the limbs and trunk of seborrhoeic subjects.

Differential Diagnosis

The importance of distinguishing primary impetigo and sycosis barbae from those with a seborrhoeic background has been emphasized. Infantile seborrhoeic dermatitis may in some instances closely simulate infantile eczema. A familial tendency to allergic disorders, and early involvement of the face rather than the scalp, favours the diagnosis of the latter.

Intertrigo in seborrhoeic subjects must be distinguished from monilial intertrigo and tinea circinata. In both seborrhoeic and monilial intertrigo the opposing surfaces are affected symmetrically in relation to the skin folds. A white sodden undermining of the edge is characteristic of monilia. Tinea circinata occurs near, rather than in, the skin flexures, and vesicles and scaling are seen at the edge of the lesion. In patients with a familial tendency to psoriasis one must always be on the watch for psoriasis occurring in the same regions as those frequently affected in seborrhoeic dermatitis. The resulting picture, with lesions in the flexures rather than on the extensor surfaces, is the exact opposite to that seen in ordinary psoriasis, and occurs characteristically in women after the menopause. Pitting or discoloration of the nails sometimes assists in the diagnosis of psoriasis.

Treatment of Seborrhoeic Dermatitis

General hygiene, such as frequent bathing and hair washing, is still the first rule to be observed by a seborrhoeic subject. Most of these people know by experience that wool "irritates" their skin, and the wearing of light clothing is an important measure in overcoming this type of skin disease. The patient should reduce his intake of carbohydrates, sweets, chocolates, and pig fat, and also avoid snacks with tea or coffee between meals.

The seborrhoeic skin is delicate, with an increased tendency to sensitization, particularly to sulphonamides or penicillin when applied locally. While sulphur and resorcinol often produce great benefit, they may induce an inflammatory reaction if applied for too long or in too high a concentration.

Mild scaliness of the scalp and presternal plaques may be removed by ung. acid. salicyl. et sulphur. (*N.F.*) rubbed in twice daily. The ointment may be washed out twice a week from the scalp with a spirit-soap shampoo. If soap irritates the skin 10% cetrimide in water can be used. A watchful eye should be kept for signs of aggravation of the disorder by overtreatment.

In the more severe cases with widespread secondary bacterial infection, particularly in the armpits and groin, daily potassium permanganate baths (1 in 8,000 in normal saline) for fifteen minutes are of value. In many cases this treatment can be augmented by an application twice a day of a watery solution of 1% gentian violet or "triple dye" (pig. violae crys. co., *B.P.C.*). A course of systemic penicillin therapy for a week, followed by the use of staphylococcal toxoid and vaccines, is of great value in cases with severe staphylococcal infection. The local use of penicillin is contraindicated as stressed above. Sycosis barbae arising on a seborrhoeic background usually responds to 1% ichthammol in lot. calamin. oleos., either smeared on four-hourly or applied as a wet dressing under a face-mask. In these cases it is helpful to keep the beard clipped short with scissors. Shaving with soap and an ordinary razor aggravates inflammation and spreads infection. An electric razor minimizes this tendency.

To the old-established plan of administration of alkalis such as mist. gent. alk. (*B.P.C.*), ½ oz. (14 ml.) three times a day, may be added an injection of crude liver extract twice weekly. Sometimes ultra-violet light therapy to the body as a whole, as well as to the infected areas, may be beneficial, or alternatively local treatment with *x* rays.

Clinical Features of Acne Vulgaris

Acne affects chiefly the face, chest, and back. The flush area of the cheeks, the centre of the forehead, the sides of the chin, and the nasolabial folds are the sites of predilection (Fig. 6). Only in severe cases does it extend widely over the face and on to the neck behind the ears or on the nuchal region. Lesions may be noted in the presternal region of the trunk, across the shoulders, and even as far as the buttocks. In some instances the lesions are seen only on the back, while in others the face alone is affected. The primary lesion is a comedo (blackhead), which is always present. The patient may also show small sebaceous retention cysts, papules, pustules, deep indurated cysts, abscesses, and scars. Comedones are flush with the skin or slightly raised, and may be found most frequently on the nose and temples. The contents can be expressed as greasy wormlike masses. The orifices of some pilosebaceous follicles become narrowed and obstruction occurs at the opening into the sebaceous gland, resulting in a retention cyst, which shows as a pinhead-sized white, glistening papule with no apparent opening from which the contents can be expressed.

FIG. 6.—Acne vulgaris. (With acknowledgment to Dr. Twiston Davies.)

The comedones become infected with acne bacillus or staphylococci of low virulence, and inflammatory changes appear around the follicle. Papule formation and perhaps pustule formation result. Many of these lesions are sterile, and the explanation of this apparent anomaly may be that the lipoid material in some follicles has induced a granuloma of the foreign-body type below the level of the skin. The cyst so produced may ultimately fibrose and visible pitted scars result.

Differential Diagnosis

The clinical picture of halogen acne occurring in seborrhoeics is identical with that of acne vulgaris. An unusual distribution on the arms, legs, and buttocks

suggests that oil, perhaps encountered at work, is a causative factor. The acne due to iodides or bromides on a normal skin looks very superficial and "stuck on." Spontaneous papules and pustules arise without the usual comedo formation. In a person with a tendency to acne, however, the diagnosis may be by deduction only.

Acne necrotica is really a bacterial folliculitis resulting in necrosis, crusting, and, finally, depressed scars, with complete destruction of the hair follicle. Pruritus is usually marked, and the site of predilection is the scalp and forehead.

Acne rosacea is better termed rosacea. Here there is an undue lability of the flush mechanism of the face. A moderate permanent erythema of the flush area appears with papulation and pustulation, but there are no comedones. It is most common in women who are seborrhoeic subjects and usually first develops in the early thirties.

Maculo-papular syphilides are increasingly rare nowadays. They may simulate acne, but the eruption, which appears suddenly, is usually widespread and there are other signs of secondary syphilis present.

Certain tuberculides produce papular and pustular eruptions on the face and the diagnosis can often be made with certainty only by means of a biopsy. Here the lesions, which affect mostly young people, have a sudden and symmetrical evolution in the form of indolent miliary nodules which may suppurate and subsequently heal with scarring. There may be no other signs of seborrhoeic diathesis and probably an absence of comedones. When a patch of the eruption is compressed with a glass slide (diascopy) brown staining like the "apple-jelly" nodes of lupus vulgaris may be detected.

Treatment of Acne Vulgaris

In planning the general treatment it is important to assess the various predisposing factors. Usually halogens and contact with oils can be ruled out. In the adolescent, general factors such as lack of exercise and excessive intake of carbohydrates and even of vitamins should be corrected. Although the vitamin-B complex is useful in combating furunculosis, it may aggravate acne vulgaris. General measures outlined under seborrhoeic dermatitis, including the use of oestrogens and thyroid extract, are useful adjuncts. The use of *x*-ray therapy, sedatives, autogenous vaccines, staphylococcal toxoid, and manganese must be considered in resistant cases.

Local treatment is directed to removing the horny plug from the orifice of the pilosebaceous follicle and preventing further obstruction. Frequent washing of the face with soap and hot water is sometimes effective in mild cases. When the back is affected, daily bathing and lathering will soften the plugs and reduce the general greasiness of the skin. Gentle friction with a loofah, huckaback towel, or hard face-flannel loosens the comedones and promotes a little healthy peeling.

Comedones which are not infected—that is, those which show only a black plug without surrounding erythema—may be expressed with an extractor. If the patient is instructed to do this herself daily, it will prevent many of the follicles becoming infected and so reduce the chance of subsequent scarring. The skin is first rubbed with either spirit or acetone and the comedone expressor is then applied. Cetrimide, 1% or even 0.5% in aqueous solution, is a useful "degreaser" and may be used for cleansing the face. An antiseptic such as hydrarg. perchlor., 1 in 5,000 in 75% spirit, should be applied to the lesions after expression.

The application or administration of antibiotics is of limited value in acne, except perhaps in a few cases in which pustule formation is pronounced, when a course of systemic penicillin may be helpful. Past. resorcin. et sulphur. (*N.F.*), smeared on at night and cleansed off with cetrimide the following morning, produces a fine superficial peeling. For daytime application the incorporation of 1% ichthammol or 1% sulphur into the patient's face-powder is useful. The scalp should be washed every four or five days and a lotion such as lot. acid. salicyl. et hydrarg. perchlor. (*N.F.*) rubbed into partings at night, twice weekly.

Hair washing with a spirit shampoo is helpful. Ultraviolet light is a useful measure in many cases. It improves the general condition of the skin and induces mild desquamation.

Treatment of Special Conditions

Sycosis Nuchae.—Epilation with forceps is beneficial and should be followed by the application of antiseptic paints, lotions, or compound "quinolor" or "vioform" ointment. Bandaging and prolonged fomentation should be avoided. Resistant cases may respond to superficial *x*-ray therapy.

Acne Conglobata.—This is notoriously resistant to treatment. The combination of subcutaneous as well as cutaneous suppuration with surrounding dense fibrosis renders topical therapy and systemic therapy with antibiotics less effective. The combination of wide incision of the large infiltrated abscesses and infiltration of the whole area with procaine penicillin, 10,000 units per ml., is probably as effective as any other treatment. Up to 5 ml. may be infiltrated weekly. This should be done only after swabs have been taken and it has been confirmed that the organisms are penicillin-sensitive. If improvement is going to occur it is usually noticeable after three or four injections.

The general practitioner can do much by regular treatment to improve the condition and minimize the scarring, but in severe cases the advice of a dermatologist should be sought.

Conclusion

This article has been planned as a revision of the established undergraduate teaching. But experience shows that, clinically, only a certain number of patients can be accurately fitted into the pictures that are traditionally recognized. Many processes in a patient's metabolism, and also the factors which influence metabolism, may affect the skin. And the appearance of many skin disorders may be influenced by a particular tendency of that patient's skin to produce an eczematous or urticarial reaction owing to a constitutional inclination towards allergic disorders. Again, the skin disorder may initiate or aggravate a mental disorder, and the effect of the disorder of the skin and the mind becomes almost inextricably mixed. The hazards of modern life and industry may produce traumatic lesions on the skin which may be followed by sensitivity reactions, and still later by changes in immunity.

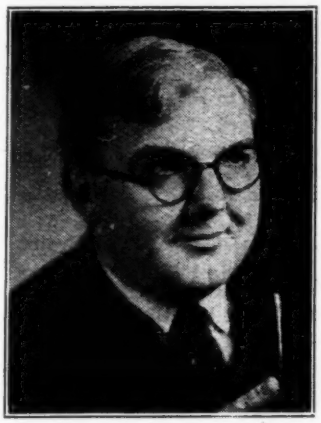
Allergic reactions, alterations in immunity, and the appearance of psoriasis or lupus erythematosus on the skin all point to the tremendous importance of always considering not only the patient's skin but his body and environment as a whole.

MEDICAL MEMBERS OF PARLIAMENT

Below are biographical notes of the members of the medical profession who were successful at the General Election held on October 25.

Dr. Charles Hill

Dr. Charles Hill (Liberal-Conservative, Luton) was born on January 15, 1904, and educated at St. Olave's School, Trinity College, Cambridge, and the London Hospital. He qualified in 1927, and graduated M.B., Ch.B. in 1929, proceeding M.D. in 1936. For a time he was a London University extension lecturer, and then spent two years as deputy medical officer of health for Oxford before coming to the B.M.A. as assistant secretary in 1932. Three years later he was made deputy secretary, and in 1944 he became secretary, which post he held until his resignation last year. He has been active in the affairs of the World Medical Association, of which body he was president in 1949–50. He was formerly chairman, and is now vice-president, of the Central Council for Health Education. He has broadcast frequently for the B.B.C. under the pseudonym of "Radio Doctor." He first stood for Parliament at the General Election of 1945, when he unsuccessfully contested the Cambridge University constituency as an Independent candidate. In 1950 he was returned for Luton with a majority of 1,086.



Dr. C. HILL (Liberal-Conservative) 26,554
W. N. Warbey (Labour) 23,842

Dr. Edith Summerskill

Dr. Edith Summerskill (Labour, Fulham West), who is 50, was a student of King's College, London, and Charing Cross Hospital. She qualified in 1924. She served on the Middlesex County Council from 1932–8, fought a Parliamentary by-election in Putney in 1934 (reducing the majority against Labour from 22,000 to 2,000), contested Bury at the 1935 General Election, and was returned in 1938 as the Member for West Fulham. In 1945 she was again returned by West Fulham, and was Parliamentary Secretary at the Ministry of Food from then until 1950, when in the next Government she became Minister of National Insurance. In 1946 Dr. Summerskill represented Great Britain at the Food and Agriculture Organization's conference at Washington, and again in 1947 in Geneva. She was one of the organizers of the Socialist Medical Association. In the 1949 New Year Honours List it was announced that Dr. Summerskill had become a Privy Councillor. Dr. Summerskill was returned in 1945 as the Member for Fulham West with a majority of 7,521. At the 1950 election she had a majority of 2,849.

Dr. EDITH SUMMERSKILL (Labour) 20.290
W. J. Brown (Ind.) 17,707
E. Walcot-Bather (L.) 1,247

Dr. S. W. Jeger

Dr. Santo W. Jeger (Labour, Holborn and St. Pancras South) is 53 and was educated at University College, Cardiff, and at the London and St. Mary's Hospitals. He qualified in 1923, and is in general practice in London. He has taken a prominent part in local government in Shoreditch and was chairman of the public health committee there. After five years on the borough council he became mayor of Shoreditch in 1930, and he has been on the London County Council since 1931. Dr. Jeger was one of the founders of the Socialist Medical Association. He first contested St. Pancras South-east in 1935, and was elected to Parliament for that constituency in 1945 with a majority of 4,710. In 1950 his majority was 1,230.

Dr. S. W. JEGER (Labour) 20,332
L. H. Gluckstein (Con.) 18,573
I. J. Hyam (L.) 1,616

Dr. Barnet Stross

Dr. Barnet Stross (Labour, Stoke-on-Trent Central) is 51 and was educated at Leeds Grammar School and at Leeds University. He graduated M.B., Ch.B. in 1925, and was engaged in general practice in Stoke-on-Trent until 1948. Dr. Stross was elected councillor of the City of Stoke-on-Trent in 1937, and in the following year he stood as Parliamentary candidate for the Hanley division of Stoke-on-Trent. In 1945 he entered Parliament, representing this division. Dr. Stross served on the Standing Committees responsible for considering the National Health Service Bill, the Nationalization of Coal Bill, and the Criminal Justice Bill. Dr. Stross was returned as the Member for Stoke-on-Trent (Hanley) in 1945 with a majority of 11,602, and as the Member for Stoke-on-Trent Central in 1950 with a majority of 16,547.

Dr. BARNET STROSS (Labour) 34,260
H. R. Fleck (Con.) 18,770

Dr. H. B. W. Morgan

Dr. H. B. W. Morgan (Labour, Warrington) was born in 1885. He was a student at Glasgow University, where he graduated M.B., Ch.B. in 1909, later taking the D.P.H. and proceeding M.D., with commendation. During the 1914–18 war he served in France, and was finally surgical specialist at the Horton War Hospital. After holding many institutional posts, Dr. Morgan was in general practice

from 1921–30. Since 1931 he has been physician to the Manor House Hospital. He was appointed medical adviser to the T.U. Congress and their specialist on industrial diseases in 1933. After fighting three general elections unsuccessfully he was returned to Parliament in 1929. He did not stand in 1931, but returned to politics in 1939 as Labour candidate for Rochdale, which constituency he represented from 1940 to 1950. He has been a member of the Council of the B.M.A. since 1940. He had much to do with the settlement of the Llanelly dispute in 1934, which led to the setting up of the joint B.M.A. and T.U.C. Committee. In 1950 Dr. Morgan was returned as the Member for Warrington with a majority of 8,752.

Dr. H. B. W. MORGAN (Labour) 26,225
Miss J. Crowther (Con.) 17,623
J. C. Park (L.) 1,537

Colonel Malcolm Stoddart-Scott

Colonel Malcolm Stoddart-Scott (Conservative, Ripon) was born in 1901. He was educated at Elmfield College, York, Ashville College, Harrogate, and Leeds University, where he graduated M.B., Ch.B. in 1926, and proceeded M.D. in 1929. He was on the resident staff of the General Infirmary at Leeds until 1939. During the war Colonel Stoddart-Scott served as the senior medical officer of the 10th A.A. Division and as D.A.D.M.S. and A.D.M.S. 48th Division. He has been honorary secretary of the Conservative Parliamentary Health Committee, and he sat on the Standing Committees which dealt with the National Health Service Bill, Analgesia in Childbirth Bill, Nurses Bill, Milk Designation Bill, and other measures. He was first elected to Parliament in 1945 as the Conservative Member for Pudsey and Otley (Yorkshire West Riding) with a majority of 1,651, and in 1950 was returned with a majority of 10,975 as Member for Ripon.

Colonel MALCOLM STODDART-SCOTT (Con.) ... 23,047
S. J. Andrews (Lab.) 10,627

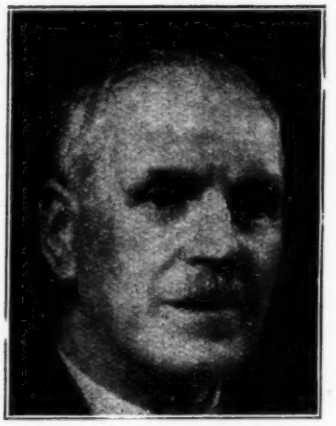
Mr. Walter Elliot

Mr. Walter Elliot (Conservative, Kelvingrove) was educated at Glasgow Academy and the University of Glasgow. He took the B.Sc. in 1910, graduated M.B., Ch.B. in 1913, and proceeded D.Sc. in 1923. The honorary degree of LL.D. has been conferred on him by the Universities of Aberdeen, Edinburgh, and Glasgow, and of Leeds and Manchester, and he is an honorary D.Sc. of the University of South Africa. From 1933 to 1936 he was Lord Rector of Aberdeen University, and he was Rector of Glasgow University from 1947 to 1950. Mr. Elliot was elected F.R.S. in 1935 and F.R.C.P. in 1940. During the war of 1914–18 he served with the R.A.M.C. Mr. Elliot was returned to Parliament as Member for the Lanark division in 1918 and again in 1923, and he was a Member for the Kelvingrove division of Glasgow from 1924 until the General Election of 1945, when he lost his seat by 88 votes to the Labour candidate. In 1946 he was returned to Westminster by the Scottish Universities after a spectacular contest in which all his opponents lost their deposits. The Representation of the People Act of 1948 abolished the university vote, and Mr. Elliot therefore returned to the Kelvingrove division of Glasgow for the election held last year, when he had a majority of 1,224. Mr. Elliot became a Privy Councillor in 1932, and from 1923 onwards he held in succession the offices of Under-Secretary of Health for Scotland, Under-Secretary of State for Scotland, Financial Secretary to the Treasury, Minister of Agriculture and Fisheries, Secretary of State for Scotland, and Minister of Health. In 1941–2 he was a director of Public Relations at the War Office.

Mr. WALTER ELLIOT (Conservative) 15,837
J. L. Williams (Lab.) 14,406

Mr. Somerville Hastings

Mr. Somerville Hastings (Labour, Barking) is consulting aural surgeon to the Middlesex Hospital. A student at Middlesex Hospital and University College, London, he graduated M.B., B.S. in 1902 and took the F.R.C.S. in 1904. Mr. Hastings has been interested in medical politics for many years. He was a member of the B.M.A. Planning Commission. In 1929 he assisted in the formation of the Socialist Medical Association, of which he was president until this year. He is also a member of the public health advisory committee of the Labour Party. He was returned as Labour M.P. for Reading in 1923. He was Parliamentary Private Secretary to the Board of Education in the first Labour Government.



Mr. Hastings has been a member of the London County Council since 1932, and he became chairman of the hospitals and medical services committee of the council in 1934, holding this post for 10 years until he became chairman of the council itself. He was a member of the Curtis Committee, and is now vice-chairman of the children's committee of the London County Council. He is at present an alderman of the council. He served in the R.A.M.C. during the 1914–18 war. At present, at the age of 73, he is chairman of the board of governors of the Hammersmith, West London, and St. Mark's Teaching Hospitals, and a member of the North-east Metropolitan Regional Hospital Board. Mr. Somerville Hastings was returned in 1945 as the Member for Barking with a majority of 18,911, and again in 1950 with a majority of 20,030.

Mr. SOMERVILLE HASTINGS (Labour) 30,486
M. T. Underhill (Con.) 11,340
N. Cork (L.) 3,387

Dr. R. F. B. Bennett

Dr. R. F. B. Bennett (Conservative, Gosport and Fareham) is 40 and was educated at Winchester, New College, Oxford, and St. George's Hospital, London. He qualified in 1937, and graduated B.M., B.Ch. in 1942. During the war he served in the R.N.V.R., and subsequently with the Fleet Air Arm, first in the Western Approaches, where he was twice torpedoed, and then in Tanganyika and Ceylon, completing more than 500 hours' flying as a pilot. Towards the end of the war he was attached to the R.N. Psychiatric Hospital at Knowle. After the war he was a psychiatrist for South Hampshire.

Dr. Bennett fought the L.C.C. elections as a Conservative in East Woolwich in 1937, and he also contested the East Woolwich constituency in the 1945 election. In 1950 he had a majority of 10,584.

Dr. R. F. B. BENNETT (Conservative)	30,727
N. Stagdon (Lab.)	20,303

Dr. A. D. D. Broughton

Dr. A. D. D. Broughton (Labour, Batley and Morley) was born on October 18, 1902. He was educated at Rossall School, Cambridge University, and the London Hospital. He qualified in 1929 and graduated M.B., B.Ch. in 1937. He took the D.P.M. in 1936 and the D.P.H. a year later. Dr. Broughton held appointments as casualty officer at Poplar Hospital and as receiving-room officer at the London Hospital before returning to Rossall School for a few years as resident medical officer. He entered general practice in Batley in 1932. During the war he served in the Medical Branch of the Royal Air Force. Dr. Broughton was elected a member of the Batley Borough Council in 1946 and held office as the vice-chairman of the public health and of the maternity and child welfare committees. He took his seat in Parliament in February, 1949, after winning the Batley and Morley by-election. He did not stand for Parliament in 1945, but was returned with a majority of 9,885 in the 1950 election.

Dr. A. D. D. BROUGHTON (Labour)	29,326
R. Northam (Con.)	19,811

Acknowledgments

The photographs of Dr. S. W. Jeger and Dr. A. D. D. Broughton are by Elliott and Fry, Ltd.; that of Colonel Malcolm Stoddart-Scott by Bassano; Mr. Walter Elliot by Davis (Streatham); Mr. Somerville Hastings by Odhams Press; Dr. H. B. W. Morgan by the *Daily Herald*; Dr. Edith Summerskill by London News Agency; Dr. Charles Hill by Cox (Luton); Dr. R. F. B. Bennett by Barrett; and that of Dr. Barnet Stross was taken privately.

"ROYAL FREE" EXTENSION

OPENING BY H.M. THE QUEEN

An extension of the Royal Free Hospital Medical School was opened by H.M. the Queen on October 24. The School is now one of the largest of the undergraduate medical schools of the University of London, and its steady expansion and development have made necessary the present extension, the second since the School was rebuilt in 1900. The extension is built on a site adjoining the main block, with which it is linked by doors on four floors.

The Queen was received on arrival by the Mayor of St. Pancras, the Chancellor of the University (the Earl of Athlone), and the Dean of the School (Miss K. G. Lloyd-Williams). In the junior common-room the Dean presented the Vice-chancellor and other officers of the University, the chairman and vice-chairman of the board of governors, and the heads of the clinical teaching departments. The opening ceremony took place in the anatomy room. The Dean, in her address of welcome, said that the new building was a far cry from the small house on the site in which, nearly 80 years ago, 14 women began their medical training. Four years later the University of London opened its medical degrees to women. To-day there were 450 students who had access to 900 hospital beds at the Royal Free, the Hampstead General, and the Elizabeth Garrett Anderson Hospitals. In 1947, in common with all the London medical schools, the School became co-educational. The new building would give better teaching facilities and also more opportunities for research work.

The Queen said that she was happy to think that her first public engagement since the King's illness should be at an institution closely connected with the relief of suffering, and it seemed a suitable place in which to pay tribute to the skill, devotion, and patience of doctors, surgeons, and nurses. "Words cannot describe our gratitude for the loving care with which the King has been surrounded. I am glad to tell you that he continues to make very steady progress."

Her Majesty went on to say that she remembered with pleasure her previous visits. The extension recalled a story of great progress in the face of many difficulties. The medical school of the Royal Free Hospital was an enduring monument to the struggle of those undaunted pioneers. Students and doctors came to the School from all over the world, and facilities for their training must match their high purpose.

The following departments in the extension were then inspected by the Queen: the pharmacology department (Dr. E. M. Scarborough), the biology department (Miss C. L. T. Lucas), the anatomy department (Professor R. E. M. Bowden), the physiology department (Professor E. M. Killick), and the chemistry department (Dr. A. Lawson). Her Majesty then proceeded across the quadrangle to the junior common-room, where she took tea and talked with the staff and students.

SHORTAGE OF DISTRICT NURSES IN LONDON

The Central Council for District Nursing in London organized a four-day exhibition last week at the Wellcome Research Institution in Euston Road, with the object of recruiting more district nurses for London. At present there are only between 300 and 400 on the roll, which means, in times of winter epidemic, that their task is almost impossible. The cases dealt with by London district nurses number 57,000 a year, and an additional 200 nurses are needed for a county population of four million. The display of domestic interiors and models was designed, therefore, to bring home to the nursing aspirant the opportunities and satisfactions of the district nurse.

The Daily Task

One saw the district nurse setting out on her round in the morning after being briefed by her superintendent, the

equipment she carried, her various duties in the homes of her patients, the improvisations she had to make, the precautions to observe, and her adaptability to the case, medical or surgical, and the nursing not only of the patient, but what Florence Nightingale called "the nursing of the room." Pictures and other reminders of Florence Nightingale were very much in evidence in the exhibition, and well they might be, for Miss Nightingale, although her popular fame rests on her achievements at Scutari, was the inspirer of district nursing in London and other cities. She once declared that she was resolved to give herself to district nursing, and, although other important duties interposed, she held the threads of the movement in her hands. One of her ablest nurses, Florence Lees, was the first superintendent of the district nursing scheme in London.

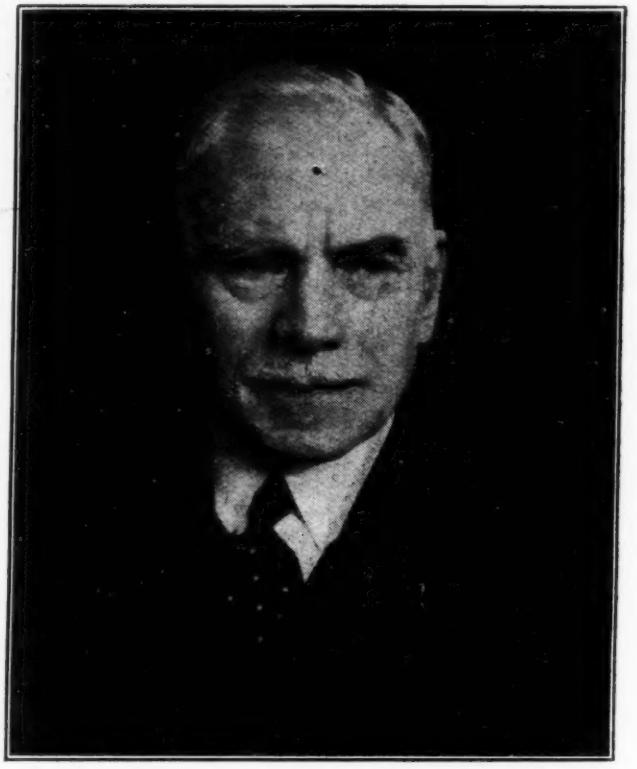
In charge of the stands at the exhibition were members of the Queen's Institute of District Nursing, founded in 1887 with a gift by Queen Victoria of £70,000—the balance of the women's jubilee fund, and the Ranyard Nurses, founded in 1857, and the Nursing Sisters of St. John the Divine, a community founded in 1848, who undertook domiciliary work in the poor quarters of London.

One of the more striking exhibits was a bedroom in a prefabricated house prepared as a midwifery room, to show the domiciliary service provided under the supervision of the London County Council by midwives of the District Nursing Association. In addition to the usual maternity outfit there was equipment for nursing premature infants at home, which is supplied by the L.C.C. at the request of the midwife. A room was devoted to surgical nursing in the home, showing how the nurse, in order not to disrupt the household more than necessary, makes use of available household utensils. Adjoining this was an exhibit of medical nursing.

The work of the district nurse in giving hypodermic and intramuscular injections was the theme at another stand, and at yet another the various social welfare services of which the district nurse is intermediary. These services, obtained through the agency of local authorities or voluntary organizations, include home helps, service of meals, occupational therapy, and various measures of rehabilitation. The training of the district nurse, involving six months' postgraduate course in training-homes, was illustrated by a sequence of photographs. Another exhibit consisted of types of uniforms worn by district nurses since the movement started; certainly there has been improvement here in comfort, efficiency, and appearance.

SIR ROBERT YOUNG AT 80

Another well-known and highly respected figure in medicine has reached the rank of octogenarian. Sir Robert Arthur Young, consulting physician to the Middlesex Hospital and Brompton Hospital, is 80 on November 6. Evidently 1871 was a good vintage year for physicians destined to be celebrated and long-lived. Sir Robert Young's name came prominently before the public recently when he was called into consultation during the King's illness. For very many years he has been one of the best-known London consultants for diseases of the chest, and although he has given up his active hospital practice he is still pursuing his profession. In addition to being consulting physician to the Middlesex and Brompton, the King Edward VII's Sanatorium, Midhurst, and the St. Saviour's and Acton Hospitals have a similar call on his services. He is frequently in attendance at medical societies, especially the Medical Society of London, where he has been Lettsomian lecturer, orator, and president. His presidential address, the theme of which was the past and present use of the stethoscope, is still well remembered after 20 years. His grave old-world manner fits in well with the figures in the famous group of eighteenth-century founders of the Society in the picture behind the president's chair.



[*Walter Stoneman, London, W.*

Sir Robert Young became a student at Middlesex Hospital in the last decade of the nineteenth century—a time, as he recalls, when the members of the medical staff, top-hatted and frock-coated, were accustomed to arrive in two-horse broughams or, more economically, in hansom cabs. The first member of the staff to use a motor-car was his highly respected senior, Sir John Bland-Sutton. Sir Robert qualified, taking first-class honours, in 1894, and proceeded M.D. (worthy of Gold Medal) the following year. He became a Member of the Royal College of Physicians of London in 1897 and Fellow in 1903. Many years later he held the position of Senior Censor of the Royal College. He has served as examiner in medicine, physiology, and materia medica and pharmacy to the Conjoint Board, and as external examiner in pharmacology and materia medica to the Universities of Birmingham and Bristol. His first published work goes back to 1897, when he translated from the German, with additions, Arnold Brass's *Atlas of Human Histology*. But most of his writings have been in the form of papers and published lectures, many of them in the Middlesex *Archives*. The *British Medical Journal* has been privileged to print many of his contributions, including his Lumleian Lectures in 1929, which took the form of a medical review of the surgery of the chest, and his Harveian Oration in 1940, on the pulmonary circulation before and after Harvey.

One of the characteristics of Sir Robert Young's work by which he will always be remembered is his thoroughness in the examination of the patient. The younger physician who leapt to the radiograph and then called in Sir Robert for help in diagnosis was over and over again courteously shown how much could be discovered by the time-honoured method of inspection, palpation, percussion, and auscultation. While he has welcomed all the modern accessories for diagnosis and treatment, he has constantly reminded his younger colleagues of the importance of the clinical instinct—what he once described as the "mind's eye"—or sixth sense, really the summation of the knowledge which comes from scientific observation, assisted by the methodical and accurate use of all the five senses and by drawing upon the stores of experience. He has suggested, while protesting

that he is no reactionary, that in these days, with the plethora of modern methods, the patient is in some danger of being over-investigated and over-treated. But it is not only for his skill and conscience as a clinician that his name will always be among the famous ones at the Middlesex and his beloved Brompton; he will be remembered also for his sympathetic manner and his power of inspiring confidence alike among his patients and the members of his own profession. Good wishes for many more years of service will go out to him on his 80th birthday.

Preparations and Appliances

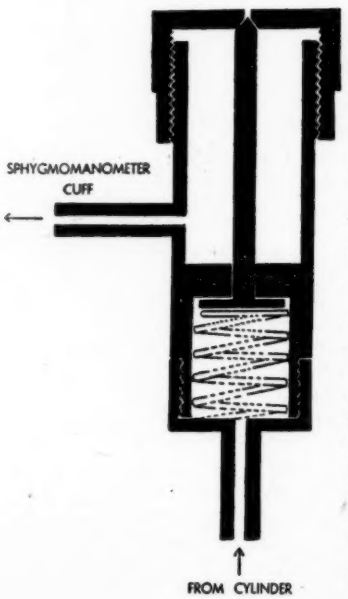
A SPHYGMOMANOMETER CUFF INFLATOR ATTACHMENT TO ANAESTHETIC MACHINES

Dr. T. M. WILLIAMS, consultant anaesthetist, Morriston Hospital, Glamorgan, writes: The small attachment to an anaesthetic machine described here has been found most useful in taking blood-pressure readings. The apparatus is attached to one of the uprights of the anaesthetic trolley, and is permanently connected with the oxygen supply, or, if preferred, the carbon dioxide supply, by means of a T-piece inserted into the coupling between the Adams reducing valve and the flowmeter. By clockwise and anti-clockwise rotation of a single control head the sphygmomanometer cuff can be smoothly inflated and deflated.

The apparatus consists of a tubular body fitted with a gas inlet at its base and a lateral outlet leading to the sphygmomanometer cuff. The body is surmounted by a knurled control head which has a small hole at its centre. Within the apparatus a disk valve divides the body into upper and lower chambers. The valve is fitted with a long stem, the bevelled tip of which fits closely into the hole in the control head. When the attachment is not in use the spring forces the disk valve against its seating and effectively seals off the pressure supply within the lower chamber.

Inflation of the sphygmomanometer cuff is carried out by clockwise rotation of the control head. The bevelled valve-stem seals off the hole in the control head and at the same time the disk valve is slowly depressed; the cuff is inflated and the mercury rises very smoothly to the figure desired. The maximum pressure obtainable, should it be required, is that of the Adams reducing valves, which on our different machines is between 180 and 250 mm. Hg (3½–5 lb. per sq. in. (0.25–0.35 kg./cm.²) approx.).

Deflation is effected by an anti-clockwise rotation of the control head. The disk valve closes, while the hole in the control head permits communication between the upper chamber and air. Either a rapid or a very fine rate of fall of the mercury can be obtained by judicious use of the control. This is the main purpose for which the attachment was designed.



The apparatus, however, is most useful in orthopaedic surgery where the cuff may be required for use as a tourniquet. All anaesthetists, I am sure, are familiar with the "leaking sphygmomanometer" and the consequent embarrassment to both surgeons and anaesthetists if the pressure should drop too low while attention is otherwise being given to the patient.

If the apparatus is used in conjunction with the oxygen supply, which is recommended, and the control head fixed in the "full-on" position, the pressure in the cuff will remain high throughout the operation and will return instantly to its original value after gross disturbances of the limb, such as painting with iodine, towelling up, etc. Once the limb is still, the pressure remains constant even though there be a small leak in the cuff connexion. It must be noted, however, that the oxygen flowmeter itself constitutes a "leak" and the highest pressure depends somewhat on the flow going to the patient, but for any given flow through the flowmeter the reading on the sphygmomanometer is reasonably constant. Where the cuff is to be used in this manner it is the practice in this hospital to employ, if possible, the same machine for all orthopaedic operations, and the Adams valves have been adjusted to give a pressure of 200 mm. Hg (4 lb. per sq. in. (0.28 kg./cm.²) approx.) when a flow of two litres of oxygen is going to the patient. When there is no oxygen flow to the patient the pressure rises to a maximum of 250 mm. Hg (5 lb. per sq. in. (0.35 kg./cm.²) approx.). Once this initial adjustment is made when fitting up the apparatus very little further attention is necessary, but of course it is advisable to check the maximum pressure from time to time.

As stated above, the attachment can be used in conjunction with the carbon dioxide supply, and it is equally effective for taking blood-pressure readings. However, when the cuff is used as a tourniquet there is occasionally a pressure drop of some 30 mm. Hg before the Adams valve opens slightly to raise the pressure in the cuff again. Should this slow drop in pressure be noticed it can be immediately rectified by a gentle finger-tap on the Adams valve. This drop does not occur when the oxygen supply is used, and, furthermore, two oxygen cylinders are available on the machine. In nine months' constant use the prototype has given no trouble.

I should like to express my sincere thanks to Mr. E. P. Childerhouse, of Medical and Industrial Equipment Ltd., 12, New Cavendish Street, London, W.1, who has very kindly made the attachment for me.

Before the 1939–45 war few facilities existed for the field medical training of Royal Army Medical Corps officers, and the lack of such training was seriously felt at the beginning of the war. Officers were dependent on receiving instruction from their commanding officer or senior administrative officer. There were no field medical units in peacetime and no demonstration equipment or teaching aids. Apart from the instructional side, there was no central organization for testing or developing new tactics, vehicles, or equipment. At the end of the war an Army Medical Directorate Committee on Post-war Field Medical Organization recommended that a school should be formed to run courses for junior and senior officers and to carry out field trials with new equipment. In August, 1949, the Field Training School was formed. It has amply justified its existence, as the following facts will indicate. The total number of officers who have passed through is 1,159; of that number 1,016 were newly joined officers, 63 were senior officers, 13 Deputy Assistant Directors Medical Services (T.A.) and Staff College nominees, and 67 T.A. officers. In addition the Director General has held two annual exercises—namely, "Britannia" and "Horatius." The Directors General of the countries representing N.A.T.O. attended the latter and largely contributed to the discussions. This year's annual exercise will be held in December to study the prevention and immediate treatment of flash burns and other injuries as a result of A.B.C. warfare, as well as the development of an adequate organization to deal with the resultant casualties.

Correspondence

A Blast of the Trumpet Against the Monstrous Regiment of Mathematics

SIR,—Considerable correspondence has recently appeared, and advice been given, about the writing of scientific papers; I have failed, however, to notice any reference to the outbreak in epidemic form of a disease known to have been endemic for years—viz., pseudo-scientific meticulosis.

The symptoms of the condition are characterized by: (*a*) Evidences of a certain degree of cerebral exaltation; (*b*) an inherent contempt for those who cannot understand logarithms; and (*c*) the replacement of humanistic and clinical values by mathematical formulae.

The physical sign most commonly met with is the outbreak of a rash of graphs, from two to ten on a paper; further, the old-fashioned graph with curves, uprights, and abscissae has gone by the board, so that now we have plates reminiscent of the blueprint of an oil-refinery; or, worse, an aggregation of dots and dashes, comparable only to the incunabula of Hittite hieroglyphics.

The systemic effects of this disease are apparent; patients are degraded from human beings to bricks in a column, dots in a field, or tadpoles in a pool; with the eventual elimination of the responsibility of the doctor to get the individual back to health.

Doubtless, since science is mensuration, a sound statistical survey of any particular form of treatment is of importance, but no statistics can cater for the psychological element in the treatment of disease. Your readers may not have heard of the patient suffering from rheumatoid arthritis who was "cured" by 20 doses of distilled water—1 ml.—the careless house-physician having failed to notice that the A.C.T.H. powder phials were in the other compartment of the box.

Sir, it is only the editors of our medical journals who, by taking a firm line, can save the sanity of the practising physician or surgeon who does not understand "these damned dots." Can we ask you to help us?—I am, etc.,

Sunderland. W. GRANT WAUGH.

Cortisone and Addison's Disease

SIR,—In "Any Questions?" (September 22, p. 746) it is stated that a man aged 43, diagnosed as having Addison's disease and discharged from hospital with a deoxycortone implant, still has considerable weakness of the legs and tachycardia on exertion. In the answer it is suggested that these symptoms may be due to excessive potassium excretion. This is true; but since he apparently had these symptoms before deoxycortone therapy was commenced, when he probably had some degree of potassium retention, it is more likely that they are due to persisting 11-oxysteroid insufficiency, and I would therefore suggest that, before removing the implant, cortisone treatment be tried. Although the general asthenia of Addison's disease can be considerably mitigated by correcting the electrolyte imbalance with deoxycortone and a high salt intake, treatment with cortisone will usually further improve the capacity for sustained muscular work, and in contradistinction to deoxycortone it will correct the anaemia and hypoglycaemia which are frequently present in Addison's disease and which may well cause tachycardia on exertion.

Although cortisone is still very scarce in the United Kingdom it would seem that a restricted supply might be more properly allocated to improving the rehabilitation of those Addisonian patients who require complete replacement therapy than in treating rheumatoid arthritis or other collagen diseases. This is because an Addisonian who is already on deoxycortone therapy will usually require only 12.5 to 25 mg. (half to one tablet) daily, provided he does not encounter an infection or other form of stress which may precipitate a crisis. In contrast to this, nearly all the other diseases which can temporarily be held in abeyance with cortisone require a maintenance dosage of around 100 mg. per day.—I am, etc.,

Merck and Co., Montreal. J. H. LAURIE, Medical Director.

Acrosclerosis

SIR,—Dr. A. S. Ramsey, in his excellent review of three cases of acrosclerosis (October 13, p. 877), suggests that this condition is a disease of adaptation and would probably respond to cortisone therapy. I entirely agree with the views expressed by Dr. Ramsey, and have recently observed the effects of A.C.T.H. and 3-hydroxy-2-phenyl cinchoninic acid (H.P.C.) upon the course of this disease. My experience of this form of treatment is limited to one case, which was reviewed in some detail a few months ago (Littler, T. R., and Canter, S., *Lancet*, 1951, **1**, 139).

10 mg. A.C.T.H. administered by the intramuscular route four times a day produced a prompt and beneficial response. Raynaud's phenomena disappeared entirely on the third day after the commencement of treatment, the patient's extremities becoming warm and flushed. After ten days' treatment the patient had gained 3 lb. (1.3 kg.) in weight, and was able to perform rather clumsy movements for the first time in four years. She also experienced a remarkable sense of well-being, in sharp contradistinction to her miserable and apathetic outlook prior to commencing treatment.

My impression of the promising results recorded in the above investigation is that further trial of cortisone and A.C.T.H. is desirable. Early diagnosis and treatment are essential, as it seems unlikely that either hormone will benefit long-standing cases. As in gross rheumatoid arthritis with severe deformity due to destruction and ankylosis of articular surfaces, similar irreversible changes may occur in the waxy "hidebound skin" associated with long-standing acrosclerosis. The effect of H.P.C. on this disease is in my experience in no way comparable to that of A.C.T.H.

In the same issue (p. 873) Drs. S. C. Truelove and H. M. Whyte describe in detail visceral involvement, especially of the oesophagus, in acrosclerosis. I have seen two cases with oesophageal lesions. In one, *x*-ray examination after a barium swallow revealed the oesophagus to be a semi-rigid tube filled with air. No visible peristaltic contractions were detected throughout its length.—I am, etc.,

Birkenhead. T. R. LITTLER.

Proper Use of Insecticides

SIR,—Dr. F. P. Coyne, in discussing the inheritance of resistance to insecticides in the housefly (October 13, p. 911), states that, when a large proportion of resistant individuals has been produced by the use of insecticides, breeding for several generations without insecticides will lead to a steady increase of non-resistant flies in the population, since the resistance factor is recessive.

This presumption is based on a simple though common fallacy. As soon as any evolutionary force such as selection or mutation has ceased to act on a gene in a reasonably large population, equilibrium between the frequencies of that gene and its allele will be reached, in the case of autosomal genes after one generation of random mating. The fact of one of the genes being dominant or recessive does not constitute an evolutionary force, or in other words mere dominance will not lead to increase in a gene frequency in a population any more than recessiveness will lead to its decrease.

The phenomenon in which Dr. Coyne believes would lead to the disappearance of all recessive genes which do not owe their continued existence to selection pressure or a high mutation rate. For example, the blood group O, which is recessive to groups A and B, would long ago have disappeared from the human race in the absence of evolutionary forces tending to preserve it.—I am, etc.,

Moreton-in-Marsh, Glos. E. H. EASON.

Bornholm Disease

SIR,—Following the report of Drs. J. B. M. Davies and J. F. Warin on an outbreak of Bornholm disease in Oxford (October 20, p. 948), some account of cases from a similar epidemic which occurred in Birmingham during the months of July and August may be of interest. Between July 16 and August 7 11 cases were observed in one general practice, and I understand that this experience was by no means unique.

The first case seen was that of a young man who presented with a temperature of 100° F. (37.8° C.), tachycardia, vomiting, and acute pain in the right chest and upper abdomen. The pain was related to breathing and referred to the right shoulder. No physical signs were found in the lungs, though there was tenderness under the right costal margin. A tentative diagnosis of diaphragmatic pleurisy was made, but as a high perforation could not be excluded he was admitted to hospital for examination.

During the following week other, but milder, cases were seen, which gave the clue to the diagnosis in the first case, whose symptoms cleared up soon after admission. As in the Oxford series, the onset of the disease was sudden, with pyrexia in all but two cases. Stabbing pain was felt in the lower chest, usually on the right though sometimes on both sides. The pain was related to breathing and lasted up to three days. Headache was a constant finding even in the two mild cases who were able to remain at work. In the pyrexial cases the disability period varied from 7 to 28 days, and recurrence of pain occurred in two patients, both of whom had had severe symptoms at the onset of the disease. Physical signs in these patients were conspicuous by their absence. In only one case a dry pleural rub was heard, a week after the onset of the disease, and this patient at the same time complained of pain in the right testicle. None of the cases showed any evidence of meningeal involvement. Family contact was observed in two instances, the interval between attacks being six days.

No specific treatment was attempted, and no opportunity existed to carry out any investigation of the possible causative virus.

The discovery of 11 cases of an uncommon condition in one practice within a relatively short period must indicate that the infection was widespread in the city at the time, and had an organization existed to correlate case reports from many such practices much useful information concerning the epidemiology of the condition might have been gained. Furthermore, a central organization which could act as a clearing-house for the observations of general practitioners might have enabled investigations at Oxford to be linked with others elsewhere in the country.

The setting up of such a general-practitioner research unit might well become an important function of the College of General Practice which was proposed in your columns by Drs. Hunt and Rose.—I am, etc.,

Birmingham. R. J. F. H. PINSENT.

SIR,—I was very interested to read the account of an epidemic of Bornholm disease in Oxford by Drs. J. B. M. Davies and J. F. Warin (October 20, p. 948). It would be of extreme interest to know the full extent of this epidemic throughout the country and to trace the origin and spread of infection.

In Wellingborough, Northamptonshire, a very extensive epidemic spread throughout the town commencing at the beginning of July, and it ceased quite suddenly on or about August 20. In my own practice I collected a series of 138 cases, and now in a neighbouring village about four miles away another smaller epidemic has been in evidence, for during the past six weeks I have noted seven cases. This town, which has a population of approximately 27,000, contains 10 doctors in six practices, and I am quite sure that if I could collect no less than 138 cases in one practice alone the total number of cases must have mounted up to a sizable aggregate which probably outnumbered any epidemic so far described in the literature. In addition, many patients have told me that they or their relatives had suffered from a short attack of what they described as "two-day 'flu," but that they did not call me in as they recovered so quickly.

My attention was first drawn to a number of cases which presented a high temperature, severe abdominal pains, and urinary frequency. The urinary symptoms and pains subsided before the usual sulphonamide treatment could have been effective, and catheter specimens of urine showed no bacteria, pus cells, or albumin. Incidentally, this urinary disturbance is a symptom which I have not encountered in any description of Bornholm disease, although it was present in a considerable number of typical cases of Bornholm disease in this epidemic.

Having been afflicted myself with this infection early in the epidemic, I became intensely curious about this unusual symptom-complex, which in different individuals produced suspicions of pleurisy, acute appendicitis, perforated gastric ulcer, poliomyelitis, and meningitis. It soon became apparent that this was something new and in epidemic form, but after missing the first few cases I gradually came to the conclusion that it was an epidemic of Bornholm disease or epidemic myalgia. A number of cases were thoroughly investigated, some of them being kept in our hospital for observation. Blood counts, differential leucocyte counts, stools, throat washings, and blood sera were obtained, and a collection of these specimens is now being investigated for evidence of the Coxsackie group of viruses. Clinically, several cases fell into the category of benign lymphocytic meningitis, but the one more or less constant feature of them all was a most severe frontal and occipital headache.

The Wellingborough epidemic occurred at a time when the majority of the inhabitants of this town leave for their summer holidays, and I was on the point of writing a letter to the *British Medical Journal* warning all general practitioners that contacts or convalescent carriers from Wellingborough might disseminate the epidemic widely, especially along the East Coast, which is the predilected area for our holiday-makers. However, I refrained because I feared the Press might pick on this item and print scare headlines.

It is hoped at a later date to publish a full description of this epidemic, including the results of treatment with the new antibiotics.—I am, etc.,

Wellingborough. A. C. R. WALTON.

SIR,—The article by Drs. J. B. M. Davies and J. F. Warin (October 20, p. 948) reminds one that an epidemic of this sort was experienced in the Kirkcaldy area during June and July, 1951. In my own general practice I attended numerous cases, mostly, but not entirely, among children. The high infectivity among families was noted, and the symptomatology was similar. For the sake of the parents' peace of mind I was obliged to send two such cases of upper abdominal pain into the children's ward of the local general hospital. The consulting surgeon later informed me that at one time he had seven such cases in the children's ward, sent in as abdominal emergencies.

A feature of one or two cases seen by me was the recurrence mentioned by Drs. Davies and Warin. I was reminded in these cases very much of dengue fever, where a similar relapse takes place.—I am, etc.,

Kirkcaldy. J. SANDILANDS.

SIR,—We wish to reply to the question raised by Dr. J. B. M. Davies and Dr. J. F. Warin (October 20, p. 948) about the incidence of Bornholm disease in County Durham. There has been a very widespread epidemic throughout South-east Durham this year, and there have also been sporadic cases of benign lymphocytic meningitis in addition to the epidemic reported at Boldon, County Durham. The first cases of Bornholm disease were seen in early April in Easington Colliery. No other epidemic reported seems to have started so early in the year.

Between April 5 and May 29 105 cases were seen in one practice. The clinical features were exactly as described in the many accounts of this disease: sudden onset of pain in one or both sides of the chest or the upper abdomen with fever and malaise, usually with rapid recovery after a few days. The typical recurrence of symptoms after a period of well-being was noted in almost all cases, some patients having as many as three recurrences. Pleural friction of short duration was heard in a minority of patients. There were no complications of any severity, although several had severe headaches as well as pains in the chest. Thirty patients had chest *x*-ray examinations during illness and no abnormality was detected. The incubation period seemed to be two to three days in many instances where a complete household was affected.

The disease spread slowly throughout the district, and by midsummer many cases were occurring in West Hartlepool, nine miles distant. In late summer the epidemic had reached Stockton, 17 miles from Easington, and at present fresh cases are still occurring in that district.

In August epidemic lymphocytic meningitis was reported from Boldon, and during the last four months six cases of benign lymphocytic meningitis, proved by lumbar puncture findings, have been seen in this district. There was no history of contact with Bornholm disease in any of these patients, however.

Many doctors in the area stated that they had seen cases of Bornholm disease, and the whole epidemic appears to have been widespread and probably involved hundreds of patients. One of the factors in the spread both locally and throughout the county was certainly the Easington Colliery disaster on May 29. Relatives came to Easington from far and wide at the time when the epidemic was at its height and presumably returned to their home areas carrying infection. Relatives from London and Coventry developed Bornholm disease during their stay in Easington.

It is clear that Bornholm disease is no longer a medical oddity in this country, and in view of its widespread incidence and its possible relationship to poliomyelitis it is suggested that a considerable increase in knowledge of the epidemiology of virus infections might result from making the disease compulsorily notifiable, at least for a few years.—We are, etc.,

W. A. BROWN.
D. M. PRINSLEY.

West Hartlepool.

College of General Practice

SIR,—I was interested to read in your pages recently a suggestion about the possible foundation of a College of General Practice. Coming as it does at a time when one reads and hears so many complaints about the lowered status and loss of prestige in general practice since the coming of the Health Scheme, this project deserves every encouragement and support from that branch of the medical profession most concerned. Of course some people will describe it as impractical idealism, but I think this same criticism among others was levelled at the R.C.O.G. when it was founded by the late Dr. Blair Bell, of Liverpool, nearly a quarter of a century ago. Who would dare to bring forward that criticism about it to-day?

In America, where they are not now even threatened with the introduction of a health scheme, there has been for some time a strongly functioning Academy of General Practice. This body has similar functions to those which have been proposed for the possible corporation in this country.—I am, etc.,

J. DESMOND O'NEILL.

Skegness.

SIR,—I should like to give active support to the proposal made by Drs. F. M. Rose and J. H. Hunt (October 13, p. 908) that a College of General Practice should be formed.

Apart from its political activities (which might so easily become predominant), there are several others by the proper discharge of which such a College could become very valuable to general practitioners and through them to a wide circle of colleagues. For as stated in the original letter such a College will not compete with the Royal Colleges; but it could supplement their work by research, teaching, and publications of a sort outside the scope of any other College.

With every general practitioner, when he dies, there is lost at least one unproved but possibly sound hypothesis unpublished. His intimate knowledge of several "queer cases," whose many details he modestly thought were not required by the medical world, dies unrecorded. During his life occasions arose when he yearned for a suitable means of publishing some suggestive line of research on a problem which he had defined but to tackle which he had neither facilities, nor time, nor the necessary training.

By becoming the repository for such hypotheses, records, and suggestions, and by suitable publication or exhibition of them, a College of General Practice would begin to establish itself in a new field. One of its publications might be aimed at enabling a general practitioner to make direct personal contact with those interested and able to help him with his research problems.

Such a College might become the most suitable body to encourage research and receive reports about non-notifiable illness and minor ailments in the home, about defects of the family health as opposed to those of the public health. Its primary field of study would be the individual and the family at home, not in hospital or the operating theatre, suffering the beginning, not the end, of ill-health.

Teaching would grow up with other activities, and at first would be largely voluntary both for the giver and receiver. But an ultimate aim would be to ensure that eventually every medical school had at least one general practitioner on its staff, giving not only lectures and tuition but also bias to the whole course. Another aim might be to improve family health by public lectures and to minimize the self-inflicted ill-health among individuals caused by ignorance. Who knows? There might even later be a demand for lectures on general practice for consultants!

During any further discussions on the subject of such a foundation it would be wise if one thought were to predominate—namely, that a College which was founded merely "to raise the status and prestige of the general practitioner" would itself surely soon founder. But a College which gave good measure to its own members through the services of a strong and efficiently organized clerical, technical, library, and medical secretariat would fulfil a great need and would soon find its own prestige enhanced.—I am, etc.,

G. I. WATSON.

Peaslake, Surrey.

SIR,—In the *Practitioner*, January, 1951, Robert Platt states it as his opinion that the main difference between medical practice to-day and 30 years ago is that "the responsibility has increased a hundred-fold." He concludes his essay, "At the moment there is no one to teach general practice." I wish to support the suggestion that there should be a College of General Practitioners.

The establishment of such a body would help to raise the status of the general practitioner in the eyes of the public, and would also increase respect for him from the houseman and the student.

The young houseman may scorn general practice because he sees its failures of diagnosis and treatment, but he can have no comprehension of how many cases of incipient cardiac failure have been successfully diagnosed and treated before the bad case in his ward was discovered; or how many cases are examined for suspected appendicitis before one is found which prompts the request for admission to hospital.

It is admitted that to-day we must run a sorting-house to discover those needing specialist investigation or treatment, but it should be remembered that we have to know something about every field of medicine, surgery, gynaecology, and obstetrics if we are not to fail our patients.

However, we should be taught to run such a sorting-house, and spend less time on how to read E.E.G.s, or to drain empyemas. In each subject—for example, diseases of the chest—while the Royal Colleges of Physicians and Surgeons should provide lectures on bronchitis, pneumonia, carcinoma, and tuberculosis, a College of General Practitioners should provide one or more lectures on productive and non-productive coughs—their differential diagnosis and treatment, including indications for confinement to bed and for *x*-ray photography of the chest; not forgetting suitable prescriptions and proprietary medicines worthy of trial.—I am, etc.,

JOAN CHAPPELL.

London, N.13.

SIR,—Professional memories are short. Perhaps Drs. F. M. Rose and J. H. Hunt (October 13, p. 908) would like to learn that about 100 years ago there nearly was a third College, a College of General Practitioners. It was a tempestuous time in medical history; reform was much in the air and the whole profession deeply stirred and at sixes and sevens. The two Royal Colleges were hedged about by their ancient charters, which they frantically defended against

all attempts at reform, with the result that in 1815 the Apothecaries Act had given the Society of Apothecaries the right to institute a qualification holding good for all England and Wales. Since that time the Society had ceaselessly striven for reform against the most strenuous resistance on the part of the other qualifying bodies in Great Britain, all of which had only a local application, the rights of the Royal Colleges only extending for seven miles round the City. There was a welter of Bills proposed and brought before Parliament—two were proposed by Warburton, two more by Hawes, while Sir James Graham, the then Home Secretary, brought forward no fewer than four Bills. All these were dropped owing to the opposition either of the Royal Colleges, the Scottish Schools, or other qualifying bodies. But the last of Sir James Graham's Bills nearly passed, for the general practitioners seemed agreed on common action. They proposed the formation of a third College, that of General Practitioners, which should absorb their champions, the Society of Apothecaries. The Society of Apothecaries on their part altruistically said they would willingly surrender their rights to any body of men who would place the true benefit of the profession and its reform before all other interests. Failing this they would continue their endeavour to introduce reforms for the improvement and elevation of the profession.

A measure of agreement had at last been reached, and Sir James was hopeful of his Bill passing, when suddenly dissension arose in the ranks of the practitioners. Those who were members of the College of Surgeons broke away from the rest and attempted to obtain the management and reform of their own College as a first step to the reform of the profession. They never succeeded, but this caused Sir James to throw up the matter of medical reform in despair. The question of a third College never arose again. The squabbling continued till the passing of the Medical Act of 1858, when the General Medical Council was called into being.—I am, etc.,

Jersey, C.I. DUNCAN C. L. FITZWILLIAMS.

Our Daily Bread

SIR,—In a recent paper Sir Edward Mellanby (October 13, p. 863) rightly draws attention to the part the medical scientist should play in deliberations on the effect that the incorporation of chemicals in food processing might have on the nation's health. Most scientists concerned with the technology of food production are now well aware of the problems involved as a result of the recent conference organized by the Food, Agriculture, and Fine Chemicals Groups of the Society of Chemical Industry (p. 905) and through earlier contributions to the *Journal of the Science of Food and Agriculture* (1950, **1**, 349; 1951, **2**, 1). The writer has repeatedly urged the need for the pharmacologist, the clinician, the nutritionist, the analytical chemist, and the food scientist to meet together in exploring the position so that the many facets involved may be understood fully by all concerned.

It is just as important for the medical scientist to appreciate the reasons why the food scientist is considering the use of a certain chemical in food processing as it is for the food scientist to seek the advice of the medical scientist on whether or not the particular use under consideration involves any hazard to health. At present there is too wide a gap between the food scientist, on the one hand, and the medical scientist on the other. In the same way that Sir Edward Mellanby expresses the view that the food scientist does not in general grasp the significance or the difficulties and complexities of living processes, so also could the food scientist claim the medical scientist is unaware of some of the controlling factors in food production.

In his consideration of the effects of flour improvers and emulsifying agents as bread improvers Mellanby concludes that because these substances increase loaf volume they cause a reduction in the nutritive value per unit volume of the loaf, in the case of flour improvers by about 15–20% and in the case of the emulsifiers from 9–20%. The interpretation of the nutritive value of bread in terms of food value per unit volume would appear illogical, for by this method a dense, imperfectly baked, indigestible loaf of small volume would be more nutritionally desirable than a well-fermented correctly baked loaf of greater volume. Again, one could take two samples of the same flour: the first when freshly milled and without the presence of any flour improver or additive of the emulsifier type could give a small loaf of poor appearance unpleasant to masticate; but the second sample of flour after keeping for several weeks would have aged in such a manner that it gave a bold loaf of good appearance and palatability and clearly of greater volume. It would appear wrong to claim that this natural process was causing a loss in nutritional value, as it would by Mellanby's method of expression in terms of energy content per unit volume. Furthermore, flours of similar nutritive composition prepared from different species of wheat or from wheats grown in various localities frequently possess different bread-making characteristics and could under exactly the same conditions of fermentation and baking give loaves of widely differing volume. Similar variations in volume can also occur simply by changing the conditions of fermentation and baking practice using the same flour. It is therefore clearly unsatisfactory to calculate nutritive values on a volume basis, and indeed their expression on a weight basis would appear far more justifiable and correct.

It should also be mentioned that a loaf, *the weight of which when sold is statutorily regulated*, is usually baked in a tin or, in the case of Scottish batch loaves, in such a manner that lateral expansion is negligible, so that the volume increase manifests itself chiefly in increased height. The ultimate effect of the increased volume resulting from the use of flour improvers and/or emulsifiers as crumb-softening agents, or even the presence of occluded air, is mainly a lengthening of the slice, to which there is also a finite limit. A person accustomed to eating four or five slices of bread at a meal will still eat the same number of slices and in effect consume the same weight of bread. Thus in fact the reduction in nutritive value caused by the use of flour improvers or emulsifiers is negligible. Whereas Mellanby calculates on the basis of certain work of mine (*Brit. J. Nutrit.*, in press) that the use as a crumb softener of 0.3% glyceryl monostearate, expressed on the flour weight, leads to a reduction of 9% in the nutritive value per unit volume of the loaf, I would claim that this volume increase makes no difference in the actual weight of bread consumed (unless it is an increase due to the greater palatability). Expressed on the bread weight, the reduction in nutritive value at this level of usage (and assuming glyceryl monostearate does not contribute to the caloric intake) would not exceed 0.25%. Similar considerations also apply to the use of flour improvers such as potassium bromate or ascorbic acid (vitamin C), the quantities used expressed as an average of the variable amounts required depending on individual flour qualities and fermentation conditions and being of the very small order of 20 parts per million parts by weight of flour.

It might be mentioned at this point that glyceryl monostearate is not a substance foreign to the body, as its presence in the bowel has been clearly demonstrated (Alvarez, W. C., *Gastroenterology*, 1947, **9**, 315), and in fact the use of this substance as a crumb-softening agent (or what is more popularly termed an antistaling agent) has been closely studied chiefly owing to this property, because available evidence indicates it as non-toxic and because in our view its use in British bread in the manner indicated would barely affect the nutritive value per unit weight of bread.

Glyceryl monostearate comprises a mixture of fat, distearate, and monostearate, some 40% of the latter being present, and it would be more correctly designated glycerinated fat. My recent work has shown clearly that if a flour improver is initially present in flour there is a synergistic effect in the presence of an emulsifier when making bread, and the amount required of each substance can be reduced considerably. Thus the quantity of glycerinated fat necessary to produce a crumb-softening effect is less than half the 0.3% mentioned above, and 4 oz. per sack (280 lb.) of flour (which yields about 380 lb. bread) is adequate. The reduction in nutritive value expressed on the bread weight would not in these circumstances amount to one-tenth part of 1%. The quantity of the flour improver—e.g., ascorbic acid or potassium bromate—would also be reduced from about 20 p.p.m. to 10 p.p.m. It will be noted from this experimental work that there must be a finite limit to the quantities of flour improver and/or crumb softener that a loaf can withstand, and in fact overtreatment is always avoided by the baker. The condition that Mellanby describes, in which he makes a summation of the effects of various improvers and additives based on scientific studies of the individual effects of each material, is one of gross overtreatment which would never happen in practice, and gives, therefore, an inaccurate picture of the manner in which these substances may be used.

It is because such misconceptions can occur that a closer co-operation between the medical scientist and the food scientist is urged, for it is clear that in a problem of such importance to the nation's food supply as the present one the more clearly we appreciate each others' methods and views the more rapidly we shall progress towards sound and just conclusions.—I am, etc.,

British Baking Industries Research Association, Chorleywood, Herts. JOHN B. M. COPPOCK.

SIR,—As a member of the British Baking Industries Research Association I have read with interest your leading article, "Our Daily Bread" (October 13, p. 896), and Sir Edward Mellanby's paper on "The Chemical Manipulation of Food" (p. 863). I refrain from comment on the opinions expressed, but I trust that you will permit me to refer to a misleading point in Sir Edward's paper on page 866. It is implicit in the whole of his argument that bread is sold to the consumer by unit volume, whereas, in fact, national bread must be sold by unit weight. The "official action" to which he refers was taken long ago, and, in its latest form, it may be found in the Bread (Control and Maximum Prices) Order.

It is not helpful to base a series of arguments on the sale of bread by volume when such a practice is illegal in this country.—I am, etc.,

Bramhall, Cheshire. S. WALTER BUTTERWORTH.

Chemical Tests for Blood in Urine

SIR,—I read with interest the paper by Drs. Harold Caplan and G. Discombe (September 29, p. 774), which leads me to describe a modification of the *o*-tolidine test which is used in our laboratories and is taught to the medical students as suitable for testing urine and other materials, such as cerebrospinal fluid, in the wards and in general practice.

Technique.—Fold a clean filter-paper lengthwise in three (5.5 cm. Whatman No. 1 is suitable). Stand the paper on its edges so that the horizontal surface is clear of the bench. Place on the paper a *very small* knife-point of solid *o*-tolidine (only a few particles of powder, less than 1 mg., is all that is required), allow to fall on to the powder one drop of well-shaken urine, and then add one drop of acid-peroxide reagent (equal parts glacial acetic acid and 3% hydrogen peroxide). If blood is present in a concentration of greater than 20 red cells/c.mm., or free haemoglobin in a concentration of more than 0.5 mg./100 ml., easily visible blue dots or a blue colour respectively will appear immediately: any colour appearing only after 15 seconds is of no significance. The test is very roughly quantitative; the following may be taken as indicating the concentration of material.

Cells	*Appearance*	*Free Haemoglobin*
10,000/mm.³ ..	Immediate deep blue lasting more than 5 min.	10 mg./100 ml.
1,000/mm.³ ..	Immediate pale blue lasting about 1 min.	1 mg./100 ml.
100/mm.³ ..	Blue dots lasting about 30 sec. ..	
10/mm.³ ..	Transient appearance respectively of scanty blue dots or of a blue tinge	0·2 mg./100 ml.

The advantage claimed for this method over the original published by H. Zwarenstein (*J. clin. Path.*, 1949, **2**, 145) is that no apparatus is needed: the filter-paper used for the test as a reaction chamber is always clean, and no washing of tiles, slides, or glass rods is required. It is necessary, for this modification, to use *o*-tolidine, and not *o*-tolidine hydrochloride, because the former is more easily obtainable pure.—I am, etc.,

London, W.1. D. N. BARON.

SIR,—I was interested to read the paper by Drs. Harold Caplan and George Discombe (September 29, p. 774). It prompts me to draw attention to a method which I have found commonly in use in the Midlands, but which seems less popular in the South. The test is often referred to as "The Cold Light Test" or "The Scotland Yard Test" (Pye's *Surgical Handicraft*, 11th ed.). It can be employed to detect blood in both urine and faeces. Two solutions are prepared as follows:

Solution 1. *o*-Amino-phthalic cyclic hydrazide (B.D.H.) 0.5 g.
Anhydrous sodium carbonate .. .. 10 g.
40% sodium hydroxide .. .. .. 12.5 ml.
Distilled water .. .. 200 ml.
Store in a dark bottle.

Solution 2. 10 volumes hydrogen peroxide.

1 ml. solution 1 is added to 5 ml. urine or faecal suspension. After shaking for several minutes, the tube is taken into a darkened room or cupboard and approximately 0.5 ml. solution 2 is added. A striking violet "cold light" appears at once and spreads throughout the tube. In strongly positive specimens it may be sufficiently intense to illuminate the immediate surroundings. This phenomenon fades on exposure to daylight. I have examined the sensitivity of this test by the method described by Dr. Caplan, and find that it will detect 3.2×10^4 red cells per ml. in uncentrifuged specimens of urine. At this dilution the cold light is readily detected, especially when the tube is inverted once. The addition of 2 mg. ascorbic acid per 100 ml. urine does not alter the sensitivity of the test. It would appear that the method is at least as sensitive as the *ortho*tolidine hydrochloride test, if not rather more so. The chief advantage appears to be in the examination of faeces, since the production of violet light in positive specimens is in no way obscured by the density of the faecal suspension. For domiciliary and ward work the test seems both sensitive and cheap. A darkened room or cupboard is usually far easier to find than a strong source of light. Solution 1 is extremely stable, and the sample used in the above tests was more than six months old.

I can find no reference to this test in Harrison (1947), and, since it is not commonly in use, it seems likely that false positives are more frequent than with other chemical tests. I should be interested to learn whether any of your readers have had experience of this test and can give any information about its reliability.—I am, etc.,

London, S.E.1. K. F. ANDERSON.

REFERENCE

Harrison, G. A. (1947). *Chemical Methods in Clinical Medicine.* Churchill, London.

Danger of Extracting Many Teeth at Once

SIR,—Dr. E. Reichenfeld (October 20, p. 969) has made an unjustified attack on the dental profession. Heavier guns than I carry will no doubt be turned upon him, but there are two points which I should like to make. Dr. Reichenfeld states that in his youth "most of the people had their own teeth in their mouths until an advanced age." Unless Dr. Reichenfeld spent his youth amongst a primitive community out of touch with civilization, this statement is demonstrably untrue. Dental disease has been rampant in Europe for at least 500 years. Then Dr. Reichenfeld asks, "If pyorrhoea is really such a common occurrence, why does the dental profession not try to cure it?" As well ask why does the medical profession not try to cure cancer? Has he never heard of Gottlieb, Orban, Fish, Broderick, and others?

If Dr. Reichenfeld would co-operate a little with his dental colleagues instead of abusing them he would avoid the pitfalls into which he has so resoundingly fallen.—I am, etc.,

Market Harborough. J. D. O'BRIEN.

SIR,—The recent correspondence in the *Journal* is interesting and Dr. A. Barham Carter (October 6, p. 850) has done a real service in recording his three cases, but, as Dr. R. S. Taylor has pointed out (October 20, p. 970), there are other factors which have to be considered.

It is true that subacute bacterial endocarditis may follow not only multiple extractions but even the extraction of

two or three teeth in patients with valvular lesions unless penicillin cover be given, but recent investigations (Lazansky, J. P., *et al.*, *J. dent. Res.*, 1949, **28**, 673) have shown that there is little difference between two or many teeth so far as the frequency of bacteriaemia is concerned.

Apart from endocarditis there are three main causes of ill-health following multiple extractions. They are: (1) Prolonged anoxia due to badly administered nitrous oxide anaesthesia in unpremedicated patients. (2) Trauma to the supporting dental tissues, often due to too rapid extracting in an effort to minimize (1). (3) Significant blood loss superimposed on a pre-existing anaemia.

A properly administered general anaesthetic does not upset a patient so much as a prolonged nasal gas. It also allows the operator to extract carefully and so minimize damage to the tissues. Also the wound edges may be sutured and complete haemostasis effected at the time of operation.

In 25 years of dental practice I have seen many people who have commenced having their teeth out by stages and who after one or two sessions have discontinued their treatment, remaining, often for years, with septic teeth in their mouths because they could not bring themselves to face the repeated ordeals.—I am, etc.,

St. Albans. E. SCHOFIELD.

SIR,—That education of the public (and of at least some medical and dental practitioners) is long overdue would seem to be one possible conclusion to be drawn from the correspondence so far published on this subject. Dr. R. S. Taylor (October 20, p. 970) points out that "multiple extractions under hospital conditions with proper post-operative rest in bed are generally free from any unpleasant sequelae." Unfortunately the majority of the public, and a not inconsiderable number of both professions, are seemingly unaware of the possible difficulties and dangers which not infrequently result from attempting this type of treatment in the dental chair. Such an operation is still too often regarded with relative indifference, the popular attitude appearing to be that the patient can pop in to the dentist, get a whiff of gas, have his teeth pulled out, and be back at work the same day.

There are, of course, many practical difficulties to be overcome before multiple extractions and similar operative procedures can be performed in hospital, and one would be unduly optimistic to hope that the public's attitude can be changed in the near future. To say the least, it will take a long time. But there seems little chance of accomplishing this so long as even a minority of dental and medical practitioners still practise, irrespective of the nature of the case, the customary whiff of gas and often inevitable smash-and-grab tactics in the dental chair, rather than skilled anaesthesia and careful surgery carried out in proper surroundings and with adequate safeguards. Education of certain sections of both professions would therefore appear to be a factor of some importance.

Dr. E. Reichenfeld (p. 969) rightly deplores the extraction of savable teeth by what he concedes is possibly a minority of the dental profession. It seems only fair to point out, however, that one does occasionally see patients suffering from a variety of conditions who have been advised by their doctors to have their teeth out as part of the hoped-for cure. In a substantial proportion of such cases no definite clinical or radiological evidence exists for this assumption, and one is sometimes forced to conclude that the doctors responsible are indulging in somewhat speculative diagnoses. The fact is that inefficiency, ignorance, and indifference are not the monopoly of the dental profession, as Dr. Reichenfeld's letter appears to imply. Once again, education in both professions would seem to be a need worthy of consideration.—I am, etc.,

Sidcup, Kent. CHARLES ROBERTSON.

SIR,—The recent correspondence on the danger of multiple extractions of teeth seems to have empirically condemned or sanctioned this practice. All Dr. A. Barham Carter's cases (October 6, p. 850) were in a special category, in which a bacterial shower in the blood stream was dangerous whether one or many teeth were extracted, and an antibiotic umbrella in these cases is essential. The main causes of the post-operative sequelae in multiple extractions of routine cases are: complete absence of pre-operative cleansing of the mouth, undue trauma of hurried extractions, and post-operative neglect. Strict avoidance of these causes, with the added security of antibiotics, can render multiple extractions reasonably safe. Dr. Barham Carter's letter also stresses the importance of the patient's past history, which should be elicited from the patient himself, or from his medical practitioner.—I am, etc.,

London, W.1. THEODORE T. SCHOFIELD.

Anaemia of Rheumatic Fever

SIR,—I read with interest Dr. J. B. Cochran's article on the anaemia of rheumatic fever (September 15, p. 637). While it seems possible that the anaemia may be due in part to the changes in plasma volume that he describes, his suggestion that this is the complete explanation cannot pass without comment. Hubbard and McKee (1939) and Gezelius (1939) have shown reticulocytosis of a significant degree immediately following the period of greatest disease activity, and in the cases I have studied this has also been true, the reticulocytes rising up to 6% in some cases. Bone-marrow studies show a low percentage of cells in the erythroid series together with defective haemoglobinization of the late normoblasts in the acute stage of the disease, and an erythroblastic marrow during recovery coincident with the reticulocytosis in the blood.

In addition to this evidence of dyshaemopoiesis, I have also found slight increase in faecal and urinary urobilinogen excretion in the acute stage of the disease, and in nine cases where the survival of transfused erythrocytes was studied in acute rheumatic fever by the modified Ashby technique there was evidence of increased red cell destruction in the first 20 to 30 days after transfusion. This finding could not be due to changes in plasma volume, as the initial donor cell count representing 100% survival was done at the height of disease activity when the plasma volume was presumably already increased, so that any error in subsequent counts taken when the E.S.R. was falling and recovery had set in would tend to be on the high side rather than the reverse, for Dr. Cochran's observations suggest that the plasma volume diminishes as the E.S.R. falls.

I would agree with Dr. Cochran that previous reports have failed to show any evidence of a haemolytic process, but these reports have been related to gross evidence of haemolysis; the relatively moderate degree of blood destruction that occurs in acute rheumatic fever would not be likely to produce clinical jaundice nor a raised serum bilirubin in the presence of a normally functioning liver.

I hope shortly to publish these observations on the cases I have studied in detail.—I am, etc.,

Boston, Massachusetts. JOHN REINHOLD.

Rupture of the Spleen

SIR,—The first case reported by Dr. J. E. S. Stephens's letter (September 22, p. 739) presumably falls in Group 1 of my classification, although he does not state whether the spleen was normal in size or not. My Cases 1 and 2 (September 8, p. 608) both occurred in England, and neither patient had ever been abroad. As already mentioned, the histology of both spleens was normal, in spite of their obvious large size. Case 3 occurred here, the patient had never had malaria (so far as he knew), and repeated examinations of the blood for malaria parasites were negative.—I am, etc.,

Georgetown, British Guiana. N. N. IOVETZ-TERESHCHENKO.

Obituary

MAY THORNE, O.B.E., M.D., F.R.C.S.I.

Dr. May Thorne, well known for her work on behalf of the Royal Free Hospital and the London School of Medicine for Women, died at her home in London on October 13 in her 91st year.

The second child of Joseph and Isobel Thorne, Mary (May) Thorne was born in China in 1861. Her mother was one of the famous pioneers who fought the early battles for the recognition of women in medicine and who helped to found the London School of Medicine for Women, becoming its first secretary in 1874. It was to help her mother in this work that May Thorne decided to qualify as a doctor. With characteristic thoroughness she felt that she would be best able to understand the problems of a medical student if she had been one herself; so, although already over 30, she qualified as a licentiate of the Society of Apothecaries in 1895, but had to travel to Brussels for her M.D. and then to Dublin for her F.R.C.S., as the Royal Colleges of England had not yet opened their doors to women.

She held various appointments in London, at the New Hospital for Women, now the Elizabeth Garrett Anderson Hospital, and elsewhere. In 1908 she followed her mother as honorary secretary of the London School of Medicine for Women. Until the first world war she was in practice in Nottingham Place and later in Harley Street, and looked after Florence Nightingale during the closing years of that remarkable life. In the 1914–18 war she served in Malta as a civilian surgeon attached to the R.A.M.C. She was one of a large party of medical women and nurses landed at Malta on the same day in 1917. The doctors in the party varied from the newly qualified to her consultant self, and it was largely owing to her tact and ability that they were able to do valuable work. She was awarded the O.B.E. for her services. After the war she did not return to private practice but bent all her energies to the furtherance of the Royal Free Hospital and its medical school and of medical women in general. She was an early president of the Association of Registered Medical Women, the precursor of the Medical Women's Federation. She served on the Board of Management of the Royal Free Hospital for forty years, only retiring in 1948 when the National Health Service began, and she never tired in her watchful vigilance over the interests of the students, past and present. She founded the Patients and Friends League and was for long the honorary secretary of the hospital, being largely responsible for the appeal department. She visited the hospital daily, always travelling by bus or on foot whatever the weather. She worked untiringly and must herself have raised many thousands of pounds. Devoid of arrogance, she was always to be seen taking an active part on flag days or jumble sales. Any recognition was always firmly refused, and it was only after her retirement that the hospital was able to give her name to one of its new wards.

Dr. Thorne never lost her interest and enjoyment of life. She fractured her femur when nearly 90, but submitted to an operation and enlivened the nurses by teaching them anatomy. Towards the end of her life she was discovered to be an excellent broadcaster. Her clear diction and beautiful voice, combined with the racy presentation of her subject, will always be remembered by those who heard her speak about Florence Nightingale. Characteristically, she declined to have her talk recorded at home, preferring to visit Broadcasting House in person.

She was a character unforgettable in her clear-sighted judgment of people and affairs, her singleness of purpose, her sense of humour and of proportion. She lived to her great age without any dimming of her wonderful personality, and, dying quietly in her sleep, was buried on St. Luke's day. A very great lady.—D. C. S.

P. G. McEVEDY, F.R.C.S.

Mr. Oliver Jelly writes: Peter McEvedy's operating was a revelation, not of how to perform a certain operation, but of what could be done with surgery in the way of converting it from craft into art and from livelihood into life. It would be a mistake to think that he was particularly humble in matters surgical: he could deal out the most devastating criticism from which no reputation was immune. "That is just the sort of surgery I don't like," he once said to me as we came away from a demonstration—a good one on any ordinary standard. And again, he was discussing the surgical treatment of ulcerative colitis, when somehow the Lane colectomy entered the argument. "Lane never really learnt how to peritonealize," and that was that. McEvedy only looked for recognition in the most difficult quarter, from his own colleagues, and here he succeeded: no others were qualified to judge. He was a surgeon's surgeon, but to call him a young surgeon's surgeon better describes the living quality of his work and its greedy reception by many disciples.

Mr. Robert V. Cooke writes: The loss of Mr. P. McEvedy will not be felt only "in Manchester and the North." For years past visiting surgeons have included Ancoats in their Manchester itinerary. There was always such a welcome for visitors and visiting clubs. A few hours with McEvedy and his colleagues never failed to be a stimulating and refreshing experience. I am sure there are very many of us who have reason to thank Peter McEvedy for much in the way of renewed inspiration, revived enthusiasm, and a determination to work harder and to work better. The sustained quality of his operative skill and his unremitting care and gentleness were a lesson to us all. Dicussions with him were always lively and provocative; there was always something to learn and much to think about. The courtesy and kindliness with which he treated every patient were exemplary and an indication of the sort of man he was. Those of us who were privileged to be at that last operating session will never forget his quiet courage. It was a magnificent thing to do, and it made one feel certain that, in the words of another friend, he well knew that peace which passeth all understanding. We shall respect his memory and continue to be thankful for the help and encouragement he gave so freely to so many of us.

Dr. ALBERT PEACOCK, lecturer in anatomy at the London Hospital Medical School, died in the London Hospital on October 14, aged 46. After qualifying from the London Hospital in 1927 he entered general practice in West Ham. His interests, however, always lay in an academic career, but it was not until after 12 successful years in general practice that he was able to fulfil his ambition and return to his teaching hospital as demonstrator of anatomy and, later, lecturer. But for his death he would have been senior

lecturer this academic year. In 1940 he took the M.B., B.S. degrees of London University, and during the course of the last 10 years he held a number of appointments besides that of lecturer in anatomy at the London Hospital. He took the degree of M.Sc.London in 1948. Between 1941 and 1943 he was supervisor of anatomical studies at Clare College, Cambridge, and from 1946 to 1948 he was lecturer in anatomy at St. Bartholomew's Hospital Medical College. At the Annual Meeting of the B.M.A. in Cambridge in 1948 he was honorary secretary of the Section of Anatomy and Anthropology. Later in that year he was appointed to a Commonwealth Teaching Fellowship in anatomy at Sydney University, where he very soon established a reputation for his knowledge and his stimulating teaching: he will always be remembered there by his students and professional friends. His contributions to the literature were varied and valuable, and his observations on the pre- and post-natal development of intervertebral disks led to his being regarded as an authority on this subject. It is to be regretted that he was not spared to continue his studies in this field and see in print his latest work, which, in spite of his increasing weakness, he insisted on continuing and discussing to the very end. His fascinating way of teaching inspired enthusiasm in all. The large forceps he used when demonstrating, his excellent diagrams, his familiar mannerisms, and the personal touch of his teaching will be remembered by all those who were fortunate enough to be his students. His interests were widespread: his knowledge of languages and literature was extensive, and he was an authority on his great hobby, music. To his wife, who was known to many of his pupils, our deepest sympathy is extended.—D. L. W.

An Australian postgraduate in London writes: The recent death of Dr. Albert Peacock has been a sad loss for many Australian postgraduates, for to them he had been friend, teacher, and counsellor. Before accepting a Commonwealth Fellowship at the University of Sydney, Dr. Peacock was well known in Australia for his keen interest in Australian postgraduates studying in London. On his arrival in Sydney his superb lecturing, clear and concise, soon commanded the respect and admiration of student and postgraduate alike, but it was in the dissecting-room that we knew him best. Here he showed to the full his mastery of anatomy and his extraordinary gift of teaching, the latter being in part due to his friendliness and ease of manner and no less to his many colourful mannerisms. Armed with an outsize pair of forceps, he conducted his daily tutorials on the body for hours without evidence of fatigue and kept the interest of students alive by interpolating anecdotes on any subject from music to comparative anatomy. His intense interest in anatomy and his extraordinary gift of presentation of the subject imbued both students and postgraduates with a zeal little less than his own, and it became commonplace for them to remain in discussion throughout the lunch hour. His personal interest in them and the facility he had for remembering them by name ensured his popularity; but it was his charm and wit, together with a wide knowledge of Australian history, flora, and fauna, that cemented his position as favourite with the students. After his return to London, Dr. Peacock's office and home became the first ports of call for many Australians newly arrived in this country, and here he sacrificed his time in giving advice and guidance. For such warm hospitality his popularity grew, and there are few to whom we owe so much. Dr. Peacock will long be remembered with gratitude by many Australians, among whom he held a unique place.

An effort is being made by the Special Committee on Infant Mortality of the Medical Society of the County of New York to lower the neonatal death rate and the incidence of stillbirth in New York. A series of monthly meetings is being held, open to all members of the medical and nursing professions and medical students, at which papers are read by specialists and then discussed.

Medico-Legal

PENICILLIN DISSOLVED IN FLAXEDIL

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

At an inquest held at Ballymoney on April 12 by the coroner for County Antrim it was disclosed that two babies had died as a result of injections of penicillin which had accidentally been dissolved in "flaxedil" instead of distilled water.

Two of the babies in the nursery at the Robinson Memorial Hospital, Ballymoney, developed spots on their faces, and it was decided by the surgeon who was in charge of one of them to treat this condition by injecting penicillin. As there was some doubt whether the available penicillin was soluble or not, the surgeon and the senior staff sister decided to test it in the theatre. The surgeon assembled a sterile syringe, and the sister then handed him an ampoule of what the surgeon thought was distilled water, which he injected into the penicillin ampoule, whereupon the penicillin dissolved. Thinking the solution would be too concentrated for a baby he asked for another ampoule of distilled water, was handed another ampoule, mixed its contents with the former solution, drew 2 ml. into the syringe, and handed syringe and solution to the sister. She returned to the nursery and injected both infants, who died almost at once.

Flaxedil (gallamine triethiodide), a synthetic muscle relaxant with effects similar to those of curare, causes death in excessive doses by paralysing the muscles of respiration. A dose of 2 ml. would be fatal to an infant. It was stated in evidence that it should never be used on young children. It is similar in appearance to distilled water, and to distinguish flaxedil ampoules from ampoules of distilled water they are marked on the glass "Flaxedil" in red. Distilled water ampoules are marked on the glass in black "Water for Injection." Neither the sister nor the surgeon noticed that the ampoules they used for dissolving the penicillin were marked "Flaxedil." The sister knew that there were both distilled water and flaxedil ampoules in the theatre. The verdict of the coroner's jury was that each baby had died through misadventure, death being due to asphyxia following the injections. The jury added a rider suggesting that, as markings on glass containers are faint, such containers should be distinguished either by being made of different coloured glass or by being marked by distinct labels.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on October 18 the following degrees were conferred:

D.M.—W. A. Briscoe.
M.CH.—R. E. B. Tagart.
B.M.—Margaret E. Lloyd, J. E. Hodgkin.

In Congregation on October 23 a gift of £50,000 from Viscount Nuffield to defray capital expenditure on the extension and equipment of the Nuffield Department of Medicine and a grant of £34,500 from the University Grants Committee towards defraying the cost of erecting a medical unit at the Churchill Hospital were accepted with gratitude.

UNIVERSITY OF CAMBRIDGE

Dr. W. Russell Brain, President of the Royal College of Physicians of London, has been appointed Rede Lecturer for 1952.

UNIVERSITY OF ST. ANDREWS

On the occasion of the opening of the postgraduate series of lectures for 1951-2, the Faculty of Medicine held a dinner in Dundee to honour Sir David Henderson, who delivered the first lecture on October 18, and to welcome the new professors—W. L. Burgess, of the Chair of Social Medicine; D. M. Douglas, Chair of Surgery; and J. L. Henderson, Chair of Child Health.

UNIVERSITY OF BIRMINGHAM

Dr. O. H. Wolff has been appointed Lecturer in Paediatrics from October 1.

Dr. Vera Norris resigned the post of Senior Statistical Officer in the Department of Medical Statistics on September 30 on appointment as Medical Statistician at Maudsley Hospital.

UNIVERSITY OF LEEDS

The following appointments are announced: *Lecturer in Anatomy*, Dr. R. L. Holmes. *Lecturer in Pharmacology*, Dr. G. A. Mogey. *Senior Registrar and Tutor in Paediatrics*, Dr. B. S. Rose. *Senior Registrar and Tutor in Surgery*, Mr. G. Harrison. *Assistant Medical Officer in Department of Student Health*, Dr. S. E. Finlay.

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At a quarterly comitia of the College held on October 25, with the President, Dr. W. Russell Brain, in the chair, Dr. W. E. Lloyd, Dr. T. C. Hunt, Dr. C. Bruce Perry, Dr. Aubrey Lewis, and Dr. G. E. Godber were elected Councillors.

The following were elected representatives of the College: Sir Harold Boldero, on the Committee of Management; Professor A. A. Moncrieff, on the Central Midwives Board; the President, Sir Harold Boldero, Dr. W. G. Barnard, and Sir Allen Daley were re-elected and Dr A. M. Cooke was elected on the Standing Joint Committee of the three Royal Colleges; Dr. C. M. Hinds Howell, Dr. T. C. Hunt, Dr. J. C. Hawksley, and Dr. J. B. Harman on the Committee of Reference; and Dr. C. M. Hinds Howell and Dr. J. B. Harman on the Central Medical War Committee.

The President announced that the Jenks Memorial Scholarship had been awarded to Charles David Gascoigne Lee Shimmin, late of Epsom College.

The Registrar announced that Dr. W. R. S. Doll had been appointed Milroy Lecturer for 1953, his subject being "Bronchial Carcinoma: Incidence and Aetiology."

The following candidates, having satisfied the Censors' Board, were elected Members of the College: H. J. Bensted, L.R.C.P., P. M. F. Bishop, D.M., D. H. Bowden, M.B., B. D. Bower, M.B., T. B. Brewin, M.B., A. J. Brink, M.B., J. Butler, M.B., D. J. Conway, M.D., N. Coulshed, M.B., A. W. Downie, M.B., P. C. Elmes, B.M., M. E. Fearnley, M.B., A. W. Ferguson, M.B., J. C. Firth, M.B., R. W. Gilliatt, B.M., T. M. D. Gimlette, M.B., E. M. Glaser, M.D., A. Goldberg, M.B., J. G. Hamilton, M.D., R. P. C. Handfield-Jones, B.M., B. Hudson, M.D., S. Kaul, M.B., Lieutenant-Colonel, A.M.C., J. K. Laing, M.B., J. W. Laws, M.B., H. M. Leather, M.B., W. G. Manderson, M.B., G. M. Maxwell, M.B., J. C. Mitchell, M.D., J. G. Neville, M.B., K. M. Nuttall, M.B., T. E. Owen, M.B., R. Prasad, M.B., I. A. M. Prior, M.B., S. R. Rao, M.B., W. D. Ratnavale, M.B., L. Sefton, L.R.C.P., Joyce F. Tucker, M.B., C. E. C. Wells, M.B., G. Westbury, M.B., D. Whitehouse, M.B., M. Wilkinson, M.B., C. P. Williamson, M.B., H. G. Wilson, M.B., I. Yentis, M.D.

Licences to practise were conferred upon 149 candidates (including 23 women) who had passed the final examination in Medicine, Surgery, and Midwifery of the Conjoint Board and who have complied with the necessary bylaws: J. A. Ademiluyi, K. B. Arney, Betty Barst, D. B. Benazon, A. Bendall, M. Bloch, J. R. Blunn, M. H. B. Borthwick, S. K. Bosher, D. J. Bowerman, K. E. J. Bowers, J. W. Bradshaw, G. R. Branson, J. F. Bray, J. Burston, P. J. L. Chapman, A. I. A. Charlton, J. W. Comper, M. N. Cushnir, D. M. S. Dane, P. J. Darlaston, G. B. Davison, F. E. Day, W. C. Duncan, I. S. du Toit, P. J. Edwards, H. O. M. El-Banhawy, D. Ellis, E. W. Evans, Gwenda W. Evans, D. A. Ewing, L. G. Fallows, D. M. Fanning, J. P. Flamank, Carol A. Foxell, M. Geffen, J. A. Gobert-Jones, G. Godfrey, M. Goodman, G. W. Goulden, J. F. Goyder, J. M. Gray, R. I. Graymore, P. S. Greaves, Everel C. Green, Barbara M. Griffith-Jones, Ludwika B. Haas, Elizabeth M. Haines, G. H. Hall, J. C. Hartgill, Charlotte Hartstein, D. A. Hastings, B. H. Helal, R. G. Hepworth, P. D. Hockenhull, C. Hodgson, J. C. Holden, Stephanie Holmes, B. J. Houghton, J. D. M. Howat, Ann H. Howes, F. J. Hughes, J. R. Jaffe, R. R. Japal, D. S. Jones, G. L. Jones, S. G. Jones, A. A. Kaplan, J. G. Kenney, I. H. Kerr, R. J. Kerry, T. W. Kidd, A. K. Knowles, J. Kohári, J. L. G. Kopelowitz, M. M. Kubik, P. F. P. Lansdown, N. R. Lewis, J. A. Linden, J. Lissowski, O. K. Litherland, M. E. Lopresti, D. T. Lovell, Krystyna M. Lubomirska, Dorothy J. Lucas, P. W. Lumley, Judith Lyne, Rosemary A. Macdonald, R. E. Mackie, J. Mackett, Pamela M. McMorran, J. J. D. Macpherson, C. R. Maddock, D. Martyn-Johns, I. A. Moollan, Ann G. Morgan, June M. Morphet, S. Nairman, P. G. Newall Watson, C. H. Nemeth, J. T. Newton, L. Poller, Audrey J. Price, Zoë C. Randall, F. Reiseger, L. A. Reitsma, J. M. Roderick, E. J. Rolls, A. Ross, P. E. H. Rutter, Anne Savage, A. E. R. Scott, M. B. Scott, J. E. Shahmoon, Mary K. Sharp, T. W. Sherratt, A. Shotts, B. R. J. Simpson, B. R. Singh, Phyllis E. Slater, J. L. Somervell, G. J. Straschnov, P. H. Swinhoe, N. S. Thomas, W. W. Thompson, W. B. Thomson, A. Thorogood, N. C. Tricks, K. W. Tuleja, M. Ungar, Elizabeth J. Vaughan, D. Wakely, D. Wallace, C. J. Wardle, B. T. Warner, A. A. Waterman, L. P. E. Watson, G. D. Weeden, A. G. Wells, R. S. Wells, N. Whelan, W. J. White, B. R. Whittard, J. L. Wilkins, E. R. Wilson, D. Winter, P. Wintersgill, M. Wright, B. Young.

Diplomas in Tropical Medicine and Hygiene, in Industrial Health, in Physical Medicine, in Ophthalmology, in Child Health, in Medical Radio-diagnosis, in Medical Radiotherapy, and in Public Health were granted, jointly with the Royal College of Surgeons of England, to the successful candidates whose names were printed in the report of the meeting of the Royal College of Surgeons of England in the *Journal* of October 20 (p. 979).

A Diploma in Ophthalmic Medicine and Surgery was granted, jointly with the Royal College of Surgeons of England, to A. H. Khan.

The Services

Surgeon Rear-Admiral K. A. I. Mackenzie, C.B., K.H.P., has been promoted to Surgeon Vice-Admiral and appointed Medical Director-General of the Navy in succession to Surgeon Vice-Admiral Sir C. Edward Greeson, K.B.E., C.B., K.H.P., the appointment to take effect in March, 1952.

Major-General (temporary) A. J. Beveridge, O.B.E., M.C., and Brigadier (temporary) R. J. Rosie, late R.A.M.C., have been appointed Honorary Physicians to the King in succession to Brigadier H. T. Findlay and Major-General J. J. Magner, C.B., M.C., retired, respectively.

Air Vice-Marshal J. MacC. Kilpatrick, O.B.E., has been appointed Honorary Physician to the King in succession to Air Vice-Marshal T. C. St. C. Morton, C.B., O.B.E., who vacated the appointment on retirement from the R.A.F.

Air Commodores J. C. Neely and F. W. P. Dixon, M.B.E., have been appointed Honorary Surgeons to the King in succession to Air Commodore W. J. G. Walker, C.B.E., and Air Marshal Sir P. C. Livingston, K.B.E., C.B., A.F.C., respectively, who have vacated the appointments on retirement from the R.A.F.

A *Supplement* to the *London Gazette* has announced the following awards:

First, Second, and Third Clasps to the Territorial Efficiency Decoration.—Major (Honorary Colonel) W. R. Martine, O.B.E., T.D., R.A.M.C.

Second Clasp to the Territorial Efficiency Decoration.—Major J. B. Bishop, T.D., R.A.M.C.

First and Second Clasps to the Territorial Efficiency Decoration.—Lieutenant-Colonel G. T. Hankey, O.B.E., T.D., R.A.M.C.

First Clasp to the Territorial Efficiency Decoration.—Lieutenant-Colonel E. R. Lovell, T.D., R.A.M.C., retired, and Major H. K. Ashworth, T.D., R.A.M.C.

Territorial Efficiency Decoration.—Captains (Honorary Majors) W. G. Mills, R. Murdoch, C. R. Clayburn, D. V. Summers, and Captain A. R. Oliver, R.A.M.C.

22nd GENERAL HOSPITAL

A reunion dinner of the 22nd General Hospital, R.A.M.C., was held at Liverpool on September 29, with Colonel A. McKie Reid in the chair. Colonels S. O. Dolan and P. R. Hawe, Lieutenant-Colonel K. McL. Cobban, and Majors R. Selby, W. E. Spence, H. G. A. Almond, and A. Langford Williams, with members of the nursing staff and other ranks, were present to the total of 60. The next dinner will be held on Saturday, September 27, 1952, and inquiries should be addressed to Mr. Clifford Cooke, 17, Greenhill Avenue, Liverpool, 18.

CASUALTIES IN THE MEDICAL SERVICES

Captain GEORGE HENRY FERGUSON BEITH, R.A.M.C., who has been killed in action in Korea, was born in 1920. He received his medical education at the Royal Colleges in Edinburgh and took the Scottish Conjoint qualification in 1945. In the following year he became house-surgeon and casualty officer at the General Hospital, Nottingham. He entered the R.A.M.C. in May, 1947, as a temporary lieutenant and in the following month was granted a short-service commission. He was promoted captain in May, 1948, and retired from the Service in June, 1950, but was recalled for duty last December.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending October 13 (No. 41).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending October 13					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	41	1	20	3	1	40	5	14	4	5	968	269	40
Deaths	1	—	—	—	—	—	—	—	—	—			
Dysentery	118	21	54	—		180	17	182	4	1	358	179	44
Deaths		—		—			—		—				
Encephalitis, acute	5	—	—	—		2	—	—	—		5	1	—
Deaths		—			—		—			—			
Erysipelas			16	2	11			14	1	4			
Food-poisoning	193	27		2		214	15		—				
Infective enteritis or diarrhoea under 2 years				9	60				8	20			
Deaths	8		1	—	—	11		4	—	2			
Measles*	1,648	32	93	148	145	5,009	303	145	72	97	5,819	2,005	446
Deaths		—	—	—	—		—	—	—	1			
Meningococcal infection	35	3	18	1	2	28	3	16	1	4	57	37	28
Deaths		1	—				1	1					
Ophthalmia neonatorum	37	—	13	—	1	45	3	14	—		92	64	43
Pneumonia, influenzal	395	17	1	6		382	18	5	3		655	415	351
Deaths (from influenza)†	9	—	—	—	—	5	2	1	—	—			
Pneumonia, primary			152					130					
Deaths	136	18		12	4	123	19		7	3			
Poliomyelitis, acute:													
Paralytic	54	4	} 9	} 5	} 2	} 308	} 14	} 39	} 4	} 1	} 463	} 48	} 20
Non-paralytic	40	4											
Deaths§	2	—			—	11	1			—			
Puerperal fever			7					7					
Puerperal pyrexia‖	251	42	8	4		91	7	6	—		174	133	91
Scarlet fever	1,032	98	208	27	39	1,193	81	139	70	72	3,333	1,844	1,106
Deaths		—	1	—	—		—	—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			126	33				142	35				
(2) Tuberculosis, non-respiratory			29	4				17	3				
(1) Deaths	} 114	{ 24	14	1	6	} 134	{ 17	27	6	19			
(2) Deaths		2	3	—	2		2	2	3	3			
Typhoid fever	6	—	—	—	—	7	1	—	—	3			
Deaths¶	—	—	—	—		—	—	—	—		27	16	8
Paratyphoid fever	90	3	—	—		8	2	—	—				
Whooping-cough	1,612	77	277	54	73	2,461	231	264	30	41	2,461	1,043	875
Deaths	2	—	—	—	—	3	—	—	—	1			
Deaths (0–1 year)	187	14	23	6	4	222	21	32	8	12	361	313	222
Deaths (excluding stillbirths)	4,206	649	486	89	124	4,417	682	534	112	173	4,417	4,109	3,846
Annual death rate (per 1,000 persons living)			10·0					10·7					
Live births	6,479	1,051	808	204	358	7,439	1,320	843	216	404	9,561	7,439	6,033
Annual rate per 1,000 persons living			16·6					16·9					
Stillbirths	141	19	22			150	22	29			259	206	150
Rate per 1,000 total births (including stillborn)			27					33					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

Vital Statistics

Infectious Diseases

The incidence of infectious diseases increased slightly during the week ending October 13 in England and Wales, and rises were recorded in the number of notifications of measles 182, scarlet fever 163, acute pneumonia 85, and paratyphoid fever 59.

Only small variations occurred in the local trends of measles, the largest fluctuation being an increase of 44 in Warwickshire. The largest variations in the returns of scarlet fever were increases in London of 32 and Lancashire of 28, and a decrease of 28 in Yorkshire West Riding. Little change occurred in the local trends of whooping-cough; the largest was a rise of 24 in Yorkshire West Riding.

The number of notifications of diphtheria was 11 more than in the preceding week, and the total was the largest for 18 weeks. The only fluctuation of note in the local returns was a rise of 4 in Northumberland. All the seven cases in this county were notified in Newcastle-upon-Tyne C.B. After two and a half years' freedom from diphtheria a case was notified in Newcastle-upon-Tyne during the week ending September 8, and this has been followed by a further 18 cases up to October 13, with one death.

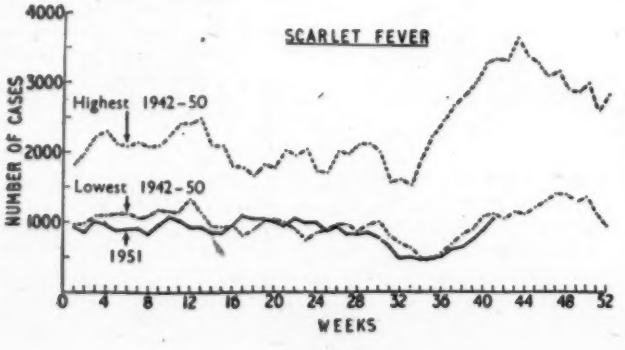
During the week 96 cases of enteric fever were notified. This is the largest total for recent years. The largest return was Yorkshire West Riding 54 (Bradford C.B. 35, Halifax C.B. 6, Huddersfield C.B. 6); most of these cases were infected in the previous week at a girls' school in Bradford C.B. Other large returns were Lancashire 14 (these cases were scattered through seven administrative areas) and Warwickshire 7 (Birmingham C.B. 5). The peak at the 43rd week in the graph opposite showing highest incidence in 1942–50 was mainly due to an outbreak in Sheffield C.B. in 1946.

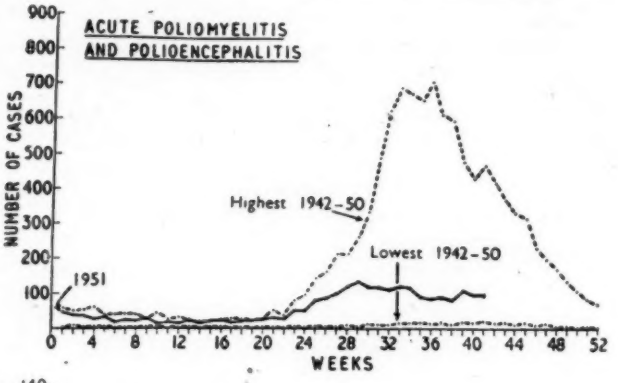
The notifications of paralytic acute poliomyelitis were 2 fewer than in the preceding week, while the number of non-paralytic cases was the same. The largest returns were Yorkshire West Riding 17 (Sheffield C.B. 8), Lancashire 10, London 8, Middlesex 7 (Hendon M.B. 3).

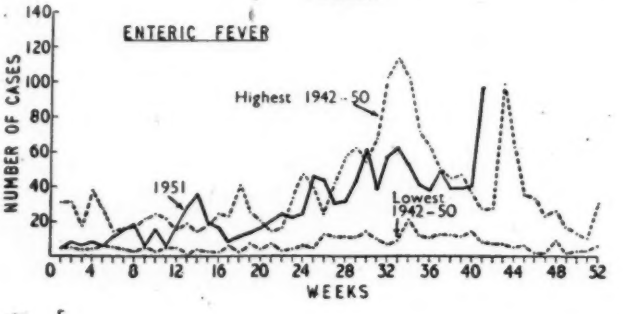
Six fewer cases of dysentery were notified during the week than in the preceding week. The chief centres of infection were London 21 (Islington 7), Lancashire 17 (Liverpool C.B. 8), Middlesex 13 (Ealing M.B. 6), Buckinghamshire 10 (Aylesbury M.B. 7).

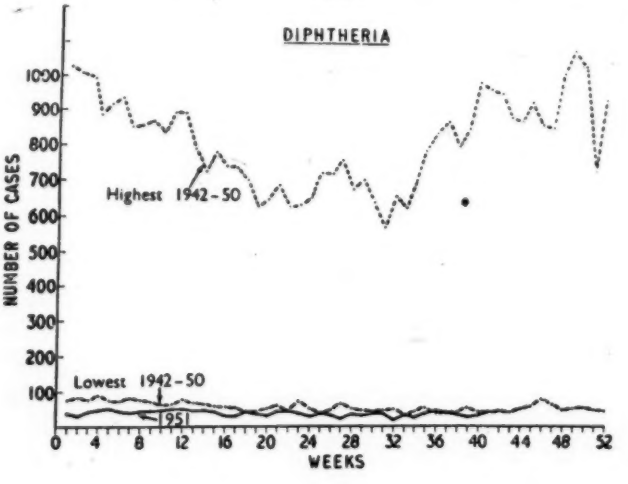
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus - - - - - - -, the figures for 1951 thus ———. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in September was 107, compared with 121 in the previous month and 220 (revised figure) for September, 1950, when the Creswell colliery disaster occurred (*Ministry of Labour Gazette*, October, 1951).

The cases of industrial diseases notified were as follows: lead poisoning 3, mercury poisoning 1, anthrax 2, epitheliomatous ulceration 18, chrome ulceration 13; total 37. There were no deaths.

Week Ending October 20

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,135, whooping-cough 1,516, diphtheria 33, measles 1,809, acute pneumonia 424, acute poliomyelitis 119, dysentery 162, paratyphoid fever 81, and typhoid fever 3.

Laboratory Diagnosis of Leptospiral Infection

In view of the large number of specimens now being sent for diagnosis of leptospiral infection to Dr. J. C. Broom at the Wellcome Laboratories for Tropical Medicine,

London, N.W.1, the Public Health Laboratory Service has arranged, at his request, for preliminary screening tests to be carried out in a number of its laboratories in different parts of the country. Difficult sera, or sera giving doubtful results, will continue to be referred to Dr. Broom. The new arrangements came into operation on November 1.

Pathologists who would like to take advantage of this may now send material to the nearest of the laboratories on the list given below:

Birmingham, Public Health Laboratory, 150, Great Charles Street, Birmingham, 3. Dr. B. R. Sandiford (Pathologist-in-Charge), Tel. Central 6921/2.

Cambridge, Public Health Laboratory, Tennis Court Road. Dr. R. M. Fry, Cambridge 55526.

Exeter, Public Health Laboratory, 7, Dix's Field. Dr. B. Moore, Exeter 54959

London, Central Public Health Laboratory, Colindale Avenue, N.W.9. Lieutenant-Colonel H. J. Bensted, Colindale 6041 and 4081.

Newcastle-upon-Tyne, Public Health Laboratory, General Hospital, Westgate Road, Newcastle-upon-Tyne, 4. Dr. A. I. Messer, Newcastle 34920.

Portsmouth, Public Health Laboratory, Block G, Infectious Diseases Hospital. Dr. K. E. Hughes, Portsmouth 74785/6/7.

Cardiff, Public Health Laboratory, Institute of Preventive Medicine, The Parade. Dr. Scott Thomson, Cardiff 8288.

Births and Deaths in September Quarter

The number of births in England and Wales during the third quarter of this year was equivalent to a birth rate of 15.2 per 1,000 population, and was 0.2 below the rate for the September quarter of last year. The infant mortality rate was 23.5 per 1,000 live births and was the lowest rate recorded for a September quarter. Stillbirths formed 21.7 per 1,000 of the total births. The death rate was 9.1 per 1,000 population, and was 0.2 below the rate for the corresponding quarter of last year.

Medical News

Streptomycin

As streptomycin sulphate is now becoming more generally available, the Ministry of Health draws attention to the suggestion made some 18 months ago that there might be danger of complications if a patient were treated first with streptomycin calcium chloride complex and then switched to the sulphate without an interval of rest. This was based on *in vitro* experiments which showed the possibility of precipitation when the two substances were mixed. It is not thought that there would be any danger in the case of intramuscular injection, but when the drugs are to be administered intrathecally caution should be exercised.

British Orthopaedic Association

The annual meeting of the British Orthopaedic Association was held on October 25–27 at Edinburgh, under the presidency of Mr. S. L. Higgs. On the first day, after a short business meeting, there was a symposium on "The Management of Rheumatoid Arthritis," followed by films of orthopaedic subjects. The second and third days were devoted to papers, of which some 15 were read on subjects ranging from aortic obstruction to vocational training of the severely disabled and including a majority on technical orthopaedic problems. Three meetings were arranged by the Clinical Research Subcommittee on "Calvé's Osteochondritis of the Spine," "Slipped Femoral Epiphysis," and "Osteochondritis Dissecans." The Fellows and associate members of the association were entertained at a reception given by the principal of Edinburgh University, Sir Edward Appleton, at which the department of physical education gave a display of Highland and country dancing and piping. There was also a dinner at the Freemasons' Hall.

Exhibitions on the History of Medicine

A new exhibition at 28, Portman Square, London, W.1, shows through a number of displays in cases some relations between British and Continental medicine in the years 1600 to 1850. In the first half of the period surgery was a French science, and books and instruments were largely imported here from Paris. But some of the influence was in the reverse direction, through such institutions as the Royal Society. Another exhibition also still being shown (upstairs) is on prehistoric medicine and surgery, and includes photographs of fossilized bacteria. The Wellcome Historical Medical Museum is open free every day, 10 a.m. to 5 p.m., but it is necessary to ring the front door bell to get in.

International Railway Medical Services Congress

The second annual congress, held in London on October 9 to 12, was attended by 39 delegates from 12 European countries, and the chief subjects of discussion were hygiene and rehabilitation.

Van Meter Prize Award

The American Goiter Association again offers the Van Meter Prize Award of $300 and two honourable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the association, which will be held at Saint Louis, Missouri, on May 1, 2, and 3, 1952, providing essays of sufficient merit are presented in competition. The competing essays may cover either clinical or research investigations; should not exceed 3,000 words in length; must be presented in English; and a typewritten double-spaced copy in duplicate must be sent to the corresponding secretary, Dr. George C. Shivers, 100, East Saint Vrain Street, Colorado Springs, Colorado, not later than March 1, 1952. The essay will be published in the annual *Proceedings* of the association.

Emergency Bed Service: Applications and Admissions

During the seven days ending October 29 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 941, of whom 88.31% were admitted.

Will

Dr. Walter Asten left £21,775. He left his property to his wife for life, and then £3,000 to the governors of the University of Birmingham, to found the Walter Asten Scholarship, to be awarded to a student or students in or entering the medical faculty, preference being given where financial position indicates the greatest need, and £100 each to various societies, including the British Medical Association Benevolent Fund. Two-thirds of the remainder to the University of Southampton for such purposes as they consider suitable in connexion with the said college, "having prior regard to the claims of research work in chemistry, biochemistry, physics, and physiology, particularly in their application to the realms of medicine and surgery."

COMING EVENTS

Church of England Hospital Chaplains' Fellowship

The annual general meeting of the Fellowship will be held on Monday, November 12, at 2.30 p.m. at the Middlesex Hospital, Mortimer Street, London, W.1. Amongst the business of the meeting will be the election of officers for the ensuing year.

Royal Medical Society

The president's annual dinner will be held in the Hall of the Royal College of Physicians of Edinburgh (9, Queen Street, Edinburgh) on Thursday, November 15, at 7.15 for 7.30 p.m. The guest of the evening will be Sir Henry Cohen. Tickets, price £2 2s., are available from the Convener, the Dinner Committee, 7, Melbourne Place, Edinburgh, 1.

Radiologists' Week-end Course

The Faculty of Radiologists has arranged a postgraduate week-end course to be held at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., on November 17 and 18, beginning at 2.30 p.m. on November 17 and at 10 a.m. on November 18. The fee is 10s. 6d.

Abortion Law Reform Association

A public meeting will be held in the Alliance Hall, Palmer Street, Westminster (opposite the West Entrance of St. James's Park tube station), on Thursday, November 22, at 7 p.m. Members, friends, and groups are invited to send in questions on abortion law reform, to be answered at the public meeting by a brains trust. The meeting will be preceded by the annual general meeting at 6.30 p.m. for members and representatives of affiliated groups.

Annual Congress of the Ophthalmological Society

This will be held at the Royal College of Surgeons of Ireland, St. Stephen's Green, Dublin, on April 17, 18, and 19, 1952. The subject for discussion will be the value of cortisone and A.C.T.H. in ocular diseases, which will be opened by Professor Alan Woods, Professor H. F. Moore, Dr. F. S. Lavery, and Mr. E. G. Mackie. Members who wish to take part in the subsequent discussion are advised to intimate their intention before the opening of the Congress: no member may speak for more than 10 minutes. Members wishing to read a short paper are asked to send the title, together with an abstract, to Mr. Harold Ridley not later than December 31 at 45, Lincoln's Inn Fields, W.C.2.

Hunterian Lecture

Professor W. Löffler, of Zurich, will deliver the Hunterian Lecture on "Endocarditis" before the Hunterian Society at the Mansion House, London, E.C., on Monday, January 14, 1952, at 8.30 p.m.

Lettsomian Lectures

Mr. R. C. Brock will deliver the Lettsomian Lectures on "The Surgery of the Heart and Great Vessels" before the Medical Society of London, 11, Chandos Street, Cavendish Square, W., on February 18 and 27 and March 3, 1952, at 8.30 p.m.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., November 5, 5.30 p.m., "*Bone Growth and Repair*," by Professor W. D. Newcomb.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—November 5, 4.30 p.m., Lecture-demonstration for postgraduates by Dr. E. Stengel.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Hammersmith Hospital, Ducane Road, W.—November 5, 4 p.m., "*Some Practical Aspects of Poliomyelitis*," by Dr. H. Stanley Banks.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—November 5, 3.45 p.m., "*The Breast and its Lymphatic Drainage, with Especial Reference to Carcinoma*," Arnott Demonstration by Mr. P. H. Mitchiner.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—November 5, 5 p.m., "*Abiotrophic Fundus Lesions*," by Professor Arnold Sorsby.

Tuesday

CHADWICK TRUST.—At the Sir Edward Meyerstein Lecture Theatre, Westminster Medical School, 17, Horseferry Road, Westminster, London, S.W., November 6, 2.30 p.m., "*The Principles of Prevention of Industrial Diseases*," by Dr. A. T. Doig.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—November 6, 5.30 p.m., "*Anatomy*," by Dr. I. Muende.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., November 6, 5 p.m., "*Trends of Opinion about the Public Health, 1901–51. 1.—The New Age*," Heath Clark Lecture by Professor J. M. Mackintosh.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—November 6, 5 p.m., "*Bacteriology of the Eye*," by Dr. A. C. Cunliffe.

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, London, W.—November 6, 5.30 p.m., neurological demonstration by Dr. C. Worster-Drought.

Wednesday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., November 7, 5.30 p.m., "*Tissue Reactions to Injury*," by Professor G. R. Cameron, F.R.S.

●DAVIDSON CLINIC, 58, Dalkeith Road, Edinburgh.—November 7, 8 p.m., "*Psychology and Literature*," by Dr. Philip Scott.

●INSTITUTE OF UROLOGY.—At St. Paul's Hospital, Endell Street, London, W.C., November 7, 4.30 p.m., "*Urological Emergencies in General Practice*," by Mr. J. G. Sandrey.

●LONDON MARRIAGE GUIDANCE COUNCIL, 78, Duke Street, Grosvenor Square, W., November 7, 6 p.m., "*Genetics and Eugenics*," by Mr. Roger Pilkington, Ph.D.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Hammersmith Hospital, Ducane Road, W.—November 7, 11.45 a.m., medical clinical pathology conference.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—November 7, 3.45 p.m., "*Myology of the Limbs*," Arnott Demonstration by Professor R. J. Last; 5 p.m., "*Congenital Syphilis*," Urology Lecture by Dr. Douglas Campbell.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—November 7, 5.30 p.m., "*Surgery of Lacrimal Sac and Ducts*," by Mr. R. P. Crick.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W.—November 7, 3.30 p.m., "*Asthma in Childhood*" (illustrated), by Dr. J. J. Kempton.

SOCIETY OF PUBLIC ANALYSTS.—At Chemical Society, Burlington House, Piccadilly, London, W., November 7, 7 p.m., ordinary meeting. Papers: "*Has the Chemical Quality of Milk Deteriorated?*" by Mr. J. G. Davis, D.Sc.; "*Some Observations on the Determination of the Activity of Rennet*," by Mr. N. J. Berridge, Ph.D.; "*The Estimation of 2:4-Dichlorophenoxyacetic Acid*," by Mr. S. W. Stroud.

Thursday

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, London, W., November 8, 8 p.m., "*The Importance of Adlerian Concepts for Modern Psychotherapy*," by Dr. Donald Blair. Discussion to be opened by Dr. P. L. Backus.

HONYMAN GILLESPIE LECTURE.—At University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh, November 8, 5 p.m., "*The Treatment of Inherited Syphilis*," by Dr. Robert Lees.

●INSTITUTE OF CHILD HEALTH, Hospital for Sick Children, Great Ormond Street, London, W.C.—November 8, 5 p.m., "*The Disorders of the Skin in Early Infancy and their Management*," by Dr. A. White Franklin.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—November 8, 5.30 p.m., "*Clinical Biochemistry in Dermatology*," by Dr. J. O. Oliver.

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool.—November 8, 8 p.m., pathological meeting. Papers: "*The Vascular Factor in the Production of Hepatic Necrosis*," by Dr. W. H. H. Andrews; "*Some Aspects and Values of Liver Biopsy*," by Dr. H. S. Pemberton, Dr. Donald Watson, and Dr. Winston Evans.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., November 8, 5 p.m., "*Trends of Opinion about the Public Health, 1901-51. 2.—The End of the First Decade*," Heath Clark Lecture by Professor J. M. Mackintosh.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—November 8, 4.30 p.m., Lecture-demonstration in Psychiatry, by Dr. M. A. Partridge.

Friday

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—November 9, 5.30 p.m., "*Erythrodermia*," clinical demonstration by Dr. D. I. Williams.

LONDON UNIVERSITY.—At Charing Cross Hospital Medical School, 62–5, Chandos Place, W.C., November 9, 5 p.m., "*Sex Differentiation in Vertebrates*," Special University Lecture by Professor E. Wolff (University of Strasbourg).

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Hammersmith Hospital, Ducane Road, W.—November 9, 11.15 a.m., surgical clinical pathology conference; 2 p.m., "*The Shoulder*," by Mr. Philip Wiles.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—November 9, 5 p.m., "*Cataract Surgery*," by Miss Mary Savory.

ROYAL INSTITUTION, 21, Albemarle Street, London, W.—November 9, 9 p.m., "*The Two Theories of Heredity*," by Mr. C. D. Darlington, D.Sc., F.R.S.

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—November 9, 8 p.m., "*Thyrotoxicosis*." Symposium.

ROYAL SANITARY INSTITUTE.—At Guildhall, Cambridge, November 9, 10 a.m. Papers on three approaches to man's welfare. (*a*) "*Improving the Environment*," by Mr. D. W. Bottom; (*b*) "*Caring for Body and Mind*," by Dr. C. G. Eastwood; (*c*) "*Research and the Wider Issues*," by Professor A. Leslie Banks.

Saturday

BIOCHEMICAL SOCIETY.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., November 10, 11.15 a.m., 302nd meeting. Symposium: "*Metabolism and Function of Nervous Tissue*."

APPOINTMENTS

CATTERALL, R. C. F., M.Chir., F.R.C.S., Assistant Orthopaedic Surgeon King's College Hospital Group.

JONES, HENRY VERNON, M.B., B.Ch., F.R.C.S.Ed., Consultant Surgeon, Barry Accident and Surgical Hospital, Glamorganshire.

LANDGREBE, F. W., D.Sc., Professor of Pharmacology, Welsh National School of Medicine, University of Wales. Dr. Landgrebe is at present Senior Lecturer in Experimental Pharmacology in the Department of Materia Medica at the University of Aberdeen.

MANCHESTER REGIONAL HOSPITAL BOARD.—*Consultant Paediatrician, Rochdale and Bury Hospitals*, B. Wolman, M.B., M.R.C.P., D.C.H. *Consultant Venereologist, Rochdale, Oldham, and Ashton Areas*, C. B. Dawson, M.B., Ch.B. *Tuberculosis Physician, Salford and West Manchester Areas*, J. F. Cotter, L.R.C.P.&S.I.

MANDIWALL, HENRY, M.B., B.S., L.D.S., Dental Consultant, West Middlesex Hospital, Isleworth, North-West Metropolitan Regional Hospital Board.

SCIENCE, PHILIP, M.D., H.M. Coroner to the City and County of Kingston-upon-Hull.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—*Assistant Chest Physician to Ham Green Sanatorium, Bristol*, D. T. Davies, M.R.C.S., L.R.C.P. *Venereologist to Bristol, North Gloucestershire, Bath, and Somerset Clinical Areas*, G. Ewart Cree, M.R.C.S., L.R.C.P. *Clinical Assistant in Ophthalmology to Cheltenham General Hospital*, B. A. E. Harley, M.R.C.S., L.R.C.P., *Senior Registrar in Thoracic Surgery to South-western Region*, D. N. Ross, M.B., Ch.B., F.R.C.S. *Orthopaedic Registrar to Mount Gold Orthopaedic Hospital, Plymouth*, J. Harding Cox, M.B., Ch.B. *Consultant Radiologist to Plymouth Clinical Area*, E. A. Waldron, L.R.C.P.&S.I., D.M.R.D.

TATTERSALL, RUTH, M.B., Ch.B., Assistant Medical Officer, Area 10, Middlesex.

WILLIAMS, JOHN, M.B., B.Ch., Assistant Chest Physician to Cardiganshire Area (West Wales).

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Chippindale.—On October 13, 1951, at Bradford, to Ruth (formerly Stevenson) M.B., D.C.H., and D. Keith Chippindale, of Rawdon, near Leeds, a brother for Peter, Simon, and Alison.

MARRIAGES

O'Brien—Craig.—On October 20, 1951, at St. James' Presbyterian Church, Huddersfield, Mr. Richard O'Brien, of Chesterfield, Derbyshire, to Dr. Elizabeth McQuilkan Davidson Craig, of Halifax, Yorks.

DEATHS

Bevan.—On October 26, 1951, at his home, 106, Marine Parade, Brighton, Sussex, Arthur Bevan, M.D., formerly of 39, Gloucester Place, London, W.

Buckley.—On October 22, 1951, at 30, Breck Road, Poulton-le Fylde, Lancs, William Henry Buckley, M.R.C.S., L.R.C.P., L.D.S., aged 84.

Cooper.—On October 25, 1951, at West Croft, Elloughton, Brough, Yorks, Wilbye Cooper, M.C., M.R.C.S., L.R.C.P.

Edwards.—On October 19, 1951, at the Cottage Hospital, Aldeburgh, Suffolk, Robert Edwards, M.D., aged 84.

Fleming.—On October 17, 1951, at Nairobi, Kenya, Alan McKinstry Fleming, M.C., M.B., B.S., D.T.M.&H.

Galstaun.—On October 17, 1951, at the White Lodge, Yelverton, Devon, Shanazar Galstaun Galstaun, M.R.C.S., L.R.C.P., D.M.R.E., F.F.R., late of Calcutta, India.

Hunter.—On October 25, 1951, at Penrose Cottage, Clifton Down, Bristol, Frank Smallpage Hunter, M.R.C.S., L.R.C.P., aged 80.

Kelf.—On October 25, 1951, at Parkstone, Dorset, Henry David Kelf, M.R.C.S., L.R.C.P., D.P.H., aged 76.

Page.—On October 24, 1951, at "Croylands," North Walsham, Norfolk, Cecil Herbert Winter Page, M.D., aged 72.

Serjeant.—On October 25, 1951, at Brighton, Robert Serjeant, M.R.C.S., L.R.C.P., of Portland House Hotel, Brighton, formerly of Clifton House, Isleworth, Middlesex, aged 79.

Taylor.—On October 22, 1951, at Southwold, Suffolk, James MacBain Taylor, M.B., Ch.B late of Oulton Broad, aged 73.

Woodhead.—On October 28, 1951, at 12, Sibson Road, Sale, Cheshire, Herbert Miall Woodnead, M.B.E., M.B., C.M., aged 91.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Tonsillitis in Children

Q.—*What is the best treatment of acute tonsillitis in children?*

A.—There are hardly any precise data about the treatment of acute tonsillitis. The few recent worth-while studies have shown that only about half the cases are streptococcal, that the complication rate is low, and that it is doubtful if chemotherapy decisively affects the results. The routine administration of potentially harmful drugs would seem to be wrong, but scepticism can be carried too far, and the writer administers sulphadimidine in standard dosage for four days to:

(1) All infants under 1 year of age (in whom the condition is uncommon anyway).

(2) All children in whom the typical clinical features, deceptive as these may be, the epidemiological evidence, or bacteriological results suggest a streptococcal infection.

(3) All cases of unusual severity.

(4) All children in whom complications are likely to be frequent or particularly unfortunate in their results, as for example those with histories of frequent otitis media or with severe congenital heart disease.

Penicillin has obvious theoretical advantages, but oral or local administration is not wholly reliable in most children and injections are not much appreciated by them. More recent antibiotics which can be taken by mouth are yet too scarce for routine use.

It is still true that general management is the most important aspect of treatment. This is well reviewed by C. H. Smith (*J. Pediat.*, 1948, **32**, 423).

Tickling

Q.—*(1) Why are some parts of the body more ticklish than others? (2) Why are some people more ticklish than others? (3) Can anything be done for people who are so excessively ticklish that, for instance, they cannot tolerate palpation of the abdomen or scrub the soles of their feet? Is there any remedy for the child who becomes hysterical when tickled by playful adults?*

A.—(1) The sensation of tickle is associated with touch sensibility, but its exact pathways and mechanism are unknown. The parts of the body where tickle can most easily be aroused in the majority of subjects have a low threshold of touch sensibility. Tickle can most easily be aroused by application of rapid, light, successive, or rhythmic stimuli which cause minimum deformation of the skin. The stimulus is thus one which tends to affect a group of superficial end organs in a particular manner at the expense of others. It is thus not unreasonable to infer that some parts of the body are more ticklish than others owing either to differences in their pattern of innervation or to variations in the structure of the skin and its appendages in relation to the nerve terminals.

(2) The reason why some people are more ticklish than others is not usually related to structural but to functional mechanisms above the level of the cord. It is comparable to pain, which is felt more acutely by some than by others. The psychological element in tickling is an important one. In some situations—for instance, when a young man is tickling or pretending to tickle a girl—erotic emotions enter the picture. The sensation of tickling can also be self-suggested—for example, when one has reason to believe, even though falsely, that an insect has dropped

down the back of one's neck. People who are abnormally ticklish are also very commonly abnormally suggestible.

(3) People who are excessively ticklish can often be persuaded to submit to examination if the skin in question is handled gently but rather more firmly than usual so that an element of pressure is added to that of touch. In particular, the examiner's hand should not move rapidly or jerkily over the skin. Soles of the feet are best cleaned by the subject himself in a standing position using pumice and soap. It must always be remembered that it is usually very difficult to tickle oneself.

Children often become "hysterical" when tickled by playful adults, and this need give no cause for alarm, but playful adults should be firmly dissuaded from this practice.

Suspension of an Artificial Leg During Pregnancy

Q.—*Is it possible for a woman to continue to wear an above-the-knee artificial limb with pelvic suspension during the latter part of pregnancy? Shoulder suspension would presumably be difficult owing to mammary enlargement.*

A.—It is possible for a woman to wear an artificial limb for a thigh amputation through all stages of pregnancy, and women have done so up to the day of entering hospital for confinement. For securing the limb, a special form of suspension has been devised so that the shoulder suspenders leave the breasts free from harmful pressure or friction; the suspenders are attached to an adjustable webbing belt from which, in turn, the limb is suspended.

Pulmonary Tuberculosis among Nursing Staff

Q.—*In a pulmonary tuberculosis hospital with 32 nurses, all Mantoux-positive and frequently radiologically examined, there have been in a period of six months two recent infections with pulmonary tuberculosis among the staff. This is unprecedented over a period of 10 years. What justification is there for regarding this as a coincidence?*

A.—One would not be justified in regarding the occurrence of two cases of pulmonary tuberculosis among the staff of the hospital as a coincidence until the following conditions had been fully investigated:

(*a*) The degree of contact between the first and second case of tuberculosis.

(*b*) The possibility of one or both the nurses who developed tuberculosis having had an early active or old quiescent lesion on joining the staff.

(*c*) The possibility of a "carrier" among the other 30 apparently healthy staff.

(*d*) The family and clinical history of the two cases of pulmonary tuberculosis.

(*e*) The age, habits, and clinical findings in each case.

It is better to assume that there is a common cause and to make a search for it than to assume that the events are a matter of coincidence.

Hormone Therapy in Azoospermia

Q.—*A man examined on account of sterility has small flabby testes, complete azoospermia (on two seminal examinations), and a variable cytology on biopsy—some tubules appearing fairly normal and showing active spermatogenesis, although most are thickened and with very few spermatic cells present. In view of the biopsy findings, is hormone therapy worth trying, or is the prognosis hopeless?*

A.—The prognosis in such a case is bad no matter whether treatment be given or not. Nevertheless it cannot be said that procreation is impossible. If any treatment is applied the most reasonable would appear to be gonadotrophin in the form of pituitary follicle-stimulating hormone (F.S.H.), 1,000 international units intramuscularly three times weekly for four to six weeks. This can do no harm, except that the protein nature of the preparation sometimes leads to local or general reactions, but it is not very likely to improve spermatogenesis.

Oestrogens and Infantile Gastro-enteritis

Q.—*In view of the water- and salt-retaining effect of oestrogens, are they of any benefit in combating the dehydration of acute infantile gastro-enteritis?*

A.—Oestrogens may lead to some degree of fluid retention, but the dehydration of infantile gastro-enteritis is due to inflammation of the intestinal mucous membrane preventing absorption of water. Oestrogens will not overcome these inflammatory effects. In any case it is unwise to administer oestrogens in large doses to infants because of the undesirability of producing effects such as pigmentation of the nipples, development of the mammary glands, and, in girls, uterine haemorrhage. More orthodox methods of treating acute gastro-enteritis are surely to be preferred.

Precautions when Giving Sulphonamides

Q.—*I was taught that a patient receiving sulphonamides should have (1) a preliminary white blood cell count and the urine tested for albumin; and (2) an alkaline mixture administered with each dose. In view of the infrequency of agranulocytosis and of renal complications during sulphonamide therapy, to what extent are the inconvenience and expense of these precautions justified in general practice?*

A.—(1) It is unnecessary to do a routine preliminary white blood cell count or a urine albumin test simply because a patient is to be given a sulphonamide, though such tests on febrile patients may often be indicated for other reasons. Agranulocytosis is extremely rare as the result of sulphonamide therapy unless the treatment is continued for longer than a week or 10 days. With the wide range of antibiotics now available such protracted sulphonamide treatment should hardly ever be necessary. Apart from sulphanilamide, sulphonamides are contraindicated in acute (Stage 1) nephritis and in other conditions associated with oliguria.

(2) The newer sulphonamide preparations, such as sulphadimethylpyrimidine ("sulphamezathine") and "sulphatriad," and the original sulphanilamide so rarely cause renal complications that it is hardly necessary to administer an alkaline mixture along with them. It is, however, desirable to render the urine alkaline if sulphathiazole or sulphadiazine is given.

Fluoride Solutions for the Teeth

Q.—*What effect have fluorides on the teeth? Would daily brushing of the teeth with a solution of sodium fluoride prevent caries, and, if so, what strength should be used?*

A.—The precise effect of fluorides on the teeth is not yet known, but their most likely role after tooth eruption is partial inhibition of bacterial growth or enzyme activity. Claims that topical applications of sodium, potassium, and other fluorides reduce the incidence or spread of caries have not been clearly substantiated, and there is no evidence that daily brushing of the teeth with such solutions would have better results.

Correction.—Dr. P. J. BURKE writes that the sixth sentence of the Addendum to his paper "A County B.C.G. Campaign" (October 13, p. 887) should read: "A small portion of those vaccinated have not yet had a post-vaccinal test, but of those who have had it 95% were positive after the six-weeks or eight-weeks interval: the 5% found negative were of course revaccinated."

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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